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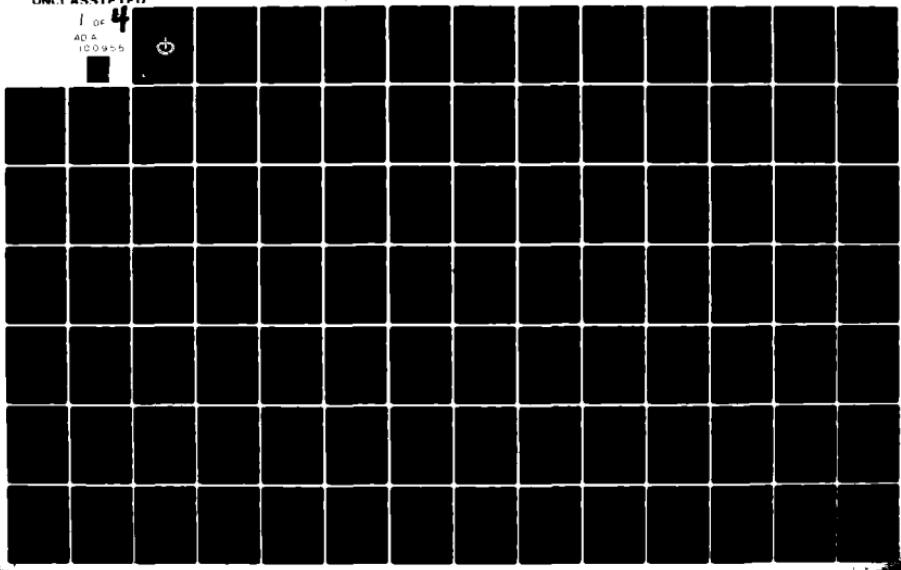
MADIGAN ARMY MEDICAL CENTER TACOMA WASH
CLINICAL INVESTIGATION SERVICE ANNUAL RESEARCH PROGRESS REPORT —ETC(U)
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CLINICAL INVESTIGATION SERVICE

ANNUAL RESEARCH PROGRESS REPORT

FISCAL YEAR 1980

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ANNUAL PROGRESS REPORT

30 SEPTEMBER 1980

DEPARTMENT OF CLINICAL INVESTIGATION
MADIGAN ARMY MEDICAL CENTER
TACOMA, WASHINGTON 98431

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19. KEY WORDS (Continue on reverse side if necessary and identify by block number) Unit summary; research protocols (objective, method, progress, status); publications; presentations.		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Subject report identifies those individuals who are conducting investigative protocols at Madigan Army Medical Center. An abstract of each protocol giving abbreviated technical objectives, methods, and progress is presented.		

ANNUAL RESEARCH PROGRESS REPORT

FISCAL YEAR 1980

DEPARTMENT OF CLINICAL INVESTIGATION
MADIGAN ARMY MEDICAL CENTER
TACOMA, WASHINGTON 98431

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council, and the Guiding Principles in the Care and Use of Animals (Appendix I), approved by the Council of the American Physiological Society. The investigators follow the recommendations from the Declaration of Helsinki (Appendix II) in the performance of investigations involving human subjects.

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FOREWORD

The Department of Clinical Investigation is reporting the results of the investigative efforts of the past year. This year has been a productive year as measured by the report of many new protocols. In our evaluation, the results are significant and impressive. The fact that others have reviewed this in the same manner can be ascertained by the many accepted publications and presentations by our investigators.

The Department of Clinical Investigation is akin to the farmer who must carefully plant his seed and give adequate water and nourishment, at the same time defending his plants from predators, small and large, and hopes to obtain a bountiful crop. In this day of austerity, it is at times tempting to divert funds and personnel to other types of utilization. A quote from Carl Sagan is very appropriate - "Without vigorous, farsighted, and continuing encouragement of scientific research, we are in a position of eating our seed corn: we may fend off starvation for one more winter, but we have removed the last hope of surviving the following winter."*

Based on the work effort, which has been continuous within our Department, presented to us from the hospital, it is apparent that there are investigators who are attempting to plant seeds of knowledge in order to have a larger harvest in the future for the betterment of their patients, their profession, and mankind.

Bruce L. Fariess
BRUCE L. FARISS, M.D.
COL, MC
Chief, Department of Clinical
Investigation

*Golden, Frederic: Carl Sagan: Astronomical Superstar. Reader's Digest, 118(706), Feb 81, p 13.

UNIT SUMMARY FY 80

1. Objective

To provide the facilities and environment to stimulate an interest in clinical and basic investigations within Madigan Army Medical Center.

2. Technical Approach

MANPOWER

<u>DESCRIPTION</u>	<u>RANK</u>	<u>MOS</u>	
Chief Fariss, Bruce L., MC	06	61C9A	
Assistant Chief Plymate, Stephen R., MC	05	61C9B	
Vet Lab Officer Ward George S., VC	04	64C00	
Bacteriologist Crumrine, Martin R., MSC	04	68A9C	
Physiologist Jacob, Willis H., MSC	04	68J9C	
Biochemist Smith, Michael L., MSC	03	68C9C	PCS Jun 80
Biochemist Little, James S., MSC	03	68C9C	
NCOIC Garretson, Charles	E6	92B40	PCS Jul 80
Med Lab Spec Darrow, Robert	E5	92B30	
OR Tech Page, Lawrence	E4	91D20	

<u>DESCRIPTION</u>	<u>RANK</u>	<u>MOS</u>
Vet Animal Spec Hayes, James	E6	91T20
Vet Animal Spec Lee, Donald R.	E4	91T20 PCS Dec 79
Vet Animal Spec Pack, Donald L.	E4	91T20 PCS Feb 80
Vet Animal Spec Gialdini, Gwen	E4	91T20
Med Tech, Supervisor Graves, James N.	GS9	00644
Med Tech Garrison, Mina J.	GS7	00644
Med Tech Matej, Louis A.	GS7	00644
Edit Asst/Steno Whitten, Nancy J.	GS6	00318
Clerk Steno Smith, Peggy	GS4	00312
Maintenance Worker Mallouf, Jerry L.	WG6	04749

<u>FUNDING</u>	
MEDCASE Equipment	\$38,504.15
Capital Equipment	4,024.95
Personnel Services (Civilian salaries)	97,649.52
Consumable Supplies	55,606.10
Contractual Services	4,481.60
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TOTAL	200,266.32

3. Progress

During FY 80 there were 194 active protocols. Of these, 128 are presently ongoing; 50 completed; and 16 terminated. In addition, administrative work has been done on 23 protocols that are pending final approval from HSC or OTSG.

There were 31 publications, 13 papers are in press, and 20 papers have been submitted that are awaiting acceptance for publication. There were 16 presentations.

4. Committee Members

Commander
Madigan Army Medical Center
BG Guthrie L. Turner, Jr., MC

CLINICAL INVESTIGATION COMMITTEE

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ACKNOWLEDGMENT

I would like to take this opportunity to thank those investigators who replied to our request promptly and, even though it is tempting, I will not castigate those investigators who were slow and at times delinquent in responding to our requests. I thank Nancy Whitten for the effort which is obvious in the compilation of this publication which is ever-increasing in size, and Peggy Smith for her support in the preparation of this publication.

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PROTOCOLS

CODES:	C - Completed	P - Publication
	O - Ongoing	PR - Presentation
	T - Terminated	SP - Submitted for publication

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1978	Characterization of the Antigenic Similarities of Group B Streptococci and <i>Streptococcus pneumoniae</i> (C) (P) (PR) (SP)	11
1969	Renal Glycosuria: Evaluation of Renal Function, Carbohydrate Metabolism and Possible Development of Diabetes Mellitus (O)	13
1974	The Effects of Chronic Hyperglycemia on Pregnancies and Fetuses in Sheep During Gestation (O) (SP)	15
1980	Adrenal Hyperplasia in Pacific Salmon (O)	17
1978	Evaluation of the Cyclic Nature of Human Semen Content (O) (PR)	18

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1979	Incidence of Hypothermia in Diabetic Ketoacidosis (C)	22
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1980	Sex Steroid Binding Globulin as a Marker of Excess Androgen Activity in Infertile Females (C) (PR) (SP)	25
1980	Effects of Exogenous Iodine on the I^{123} Uptake of Patients with Hyperthyroidism and an Elevated I^{123} Uptake (O)	26
1980	Effects of Testosterone and Estrogen Administration on Endorphin and Enkephalin Release in the Human Female (O)	27
1980	Mechanism of HCG in Spermatogenesis During Testosterone Suppression (O)	28
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SOCIAL WORK SERVICE

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DEPARTMENT OF CLINICAL INVESTIGATION

Jacob, W.H., Smith, M.L., Plymate, S.R., and Cricco, C.F.: Daily Variations in Human Semen Quality. Presented to the Pacific Coast Fertility Society Meeting, 20 Oct 79, Rancho Mirage, CA, abstract #13.

Karp, L.E., Stenchever, M.A., Plymate, S.R., Shy, K.K., Williamson, R., and Smith, D.: The Sperm Penetration Assay: A Useful Test in Assessing Male Infertility. Presented to Society for Gynecologic Investigation, Mar 80, Denver, CO.

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Ward, G.S.: Biomedical Materials. Univ of Washington, Dept of Physiology and Div of Lab Animal Medicine, Seattle, WA, 27 Nov 79.

DEPARTMENT OF EMERGENCY MEDICINE

Pryor, G.J., Kilpatrick, W.R., and Opp, D.R.: Local Anesthesia in Minor Lacerations: Topical TAC vs Lidocaine. Presented to the Emergency Medicine Annual Conference, Tucson, AZ, Apr 80.

DEPARTMENT OF MEDICINE

Reed, J.W.: Coronary Artery Disease in Young Males. Presented to the Pan-American Medical Society, Mayaguez, Puerto Rico, 16 Nov 79.

PRESENTATIONS FY 80

DEPARTMENT OF PATHOLOGY

Podgore, J.K., Belts, R., Alden, E., and Alexander, E.R.: Effectiveness of Maternal Third Trimester Erythromycin in Prevention of Infant *Chlamydia trachomatis* Infection. Presented to the 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, sponsored by American Society for Microbiology, 22-24 Sep 80, abstract #524.

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DEPARTMENT OF PEDIATRICS

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PHYSICAL MEDICINE AND REHABILITATION SERVICE

Singh, S., Dresner, M., and Saeed, M.: Bulbocavernosus Reflex in Men with Impotence. Presented to American Association of Electromyography and Electrodagnosis, 26 Sep 80, Philadelphia, PA.

Singh, S. and Kraft, G.: Total Hand "Numbness" in Carpal Tunnel Syndrome. Presented to Amer Congress Rehab Med and Amer Acad Phy Med & Rehab, 11-16 Nov 79, Honolulu, HI.

DEPARTMENT OF SURGERY

Finnerty, R.U., Buck, A.S., and Podgore, J.K.: Chlamydial Infection in Acute Epididymitis and Asymptomatic Males. NW Urological Seminar, 1 Dec 79, Third prize.

Finnerty, R.U., Buck, A.S., and Podgore, J.K.: The Role of Bacterial and Chlamydial Agents in Acute Epididymitis and the Effect of Antibiotic Therapy. Kimbrough Biologic Seminar, Nov 79, Honorable mention.

PRESENTATIONS FY 80

Surgery (Cont'd)

Hays, L.L.: The Frey Syndrome: A Review and Double Blind Evaluation of the Topical Use of a New Anticholinergic Agent. Presented to ENT Residents, University of Omaha, 2 Nov 79.

Wells, J.R., Ward, G.S., Ekland, D., Jackson, S., and Hays, L.L.: Opportunities in Microvascular Anastomosis: A Self-Instructional Method. Presented to the Annual Meeting of the American Academy of Otolaryngology, 28 Sep 80, Anaheim, CA, Scientific Exhibit #SE-27.

D E T A I L S H E E T S
F O R
P R O T O C O L S

TITLE: Characterization of the Antigenic Similarities of Group B Streptococci and *Group B Streptococci*.

PRINCIPAL INVESTIGATOR: MAJ Martin H. Crumrine, MSC

PROFESSIONAL ASSISTANTS: LTC Errol R. Alden, MC
LTC John K. Podgore, MC

WORK UNIT NO: 78/48

TECHNICAL OBJECTIVE

To further delineate the antigenic similarities between type III Group B streptococci and *Group B Streptococci*.

METHOD

1. To isolate and purify GBS antigens and *in* *vitro* antigens.
 - a. Organisms will be cultured in a chemically defined medium.
 - b. Antigens will be extracted, using several techniques, and fractionated.
 - c. Protein DNA and RNA will be removed from the carbohydrate antigens.
 - d. The antigen then will be concentrated by lyophilization.
2. The following antibodies will be produced in rabbits.
 - a. Whole cell GBS and *in* *vitro* antibody.
 - b. Antibodies against each of the type specific whole cell antigens of the 5 types of GBS and several pneumococcal types.
 - c. Antibodies against various type specific polysaccharides.
3. Comparisons of all 5 GBS types with various *in* *vitro* antisera and *in* *vitro* antigens with GBS type specific antisera and GBS whole cell antisera using the following techniques: immunodiffusion, chemiluminescence, opsonophagocytic activity, and animal protection tests.
4. To characterize the cross reactive antigenic sites using specific mono- and oligosaccharides to demonstrate the similarities of the antigenic sites.
5. To determine if any cross reactive antigens are in the pneumococcal vaccine using the techniques described above.

PROGRESS

(79 10 - 80 09) Cross-reacting antigens of *Group B Streptococci* type 14 (Pn 14) and group B streptococci type III (GBS III) were studied in detail using immunodiffusion and

Characterization of the Antigenic Similarities of Group B Streptococci and *Streptococcus pneumoniae* - Crumrine.

immunochemical techniques. Lines of identity were observed between purified type specific polysaccharide antigen of GBS III and type 14 Pn polysaccharide. Identical electrophoretic mobility was observed with the cross-reacting antigens. No other cross reactions were observed between GBS Ia, Ib, Ibc, and II and Pn types 1, 3, 4, 6, 7, 8, 9, 12, 14, 18, 19, and 23. Three other isolates and two reference cultures of GBS III exhibited the cross-reacting ag. Attempts to increase our ability to detect low levels of ab or ag using chemiluminescence, direct and indirect hemagglutination, and a slide opsonophagocytic assay were not productive.

STATUS: (C)

PUBLICATIONS:

1. Crumrine, M.H., Fischer, G.W., and Balk, M.W.: Immunochemical Cross-Reactions Between Type III Group B *Streptococcus* and Type 14 *Streptococcus pneumoniae*. *Infect Immun* 25:960-963, 1979.
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2. Crumrine, M.H., Balk, M.W., and Fischer, G.W.: Immunologic Cross-Reactivity Between Type III Group B Streptococci and Type 14 *Streptococcus pneumoniae*. American Society for Microbiology, 1978, abstract #E111.

TITLE: Renal Glycosuria: Evaluation of Renal Function, Carbohydrate Metabolism and Possible Development of Diabetes Mellitus

PRINCIPAL INVESTIGATOR: COL Bruce L. Fariss, MC

PROFESSIONAL ASSISTANT: None

WORK UNIT NO: 69/01

TECHNICAL OBJECTIVE

To study patients with renal glycosuria in an attempt to further classify these patients. More importantly, we shall attempt to distinguish those patients who may develop diabetes mellitus by studying responses to oral glucose and intravenous glucose and tolbutamide with measurement of blood and urine glucose and insulin levels. The patients will be reevaluated at yearly intervals up to five years to determine the incidence of diabetes mellitus.

METHOD

Forty patients who are found to have flat or normal oral glucose tolerance tests with renal glycosuria shall be evaluated.

Day 1: History, physical examination, routine CBC, chest x-ray, STS, regular hospital diet (300 gm CHO).

Day 2: Twenty-four hour urine for Na, K, CO₂, Cl₂, Ca, P, SGOT, alkaline phosphatase, BUN, creatinine, uric acid and serum electrophoresis. Urinary pH measured at each voiding.

Day 3: Oral glucose tolerance blood and urine glucose and plasma insulin levels.

Day 4: Intravenous glucose tolerance test (25 gm), blood and urine glucose and plasma insulin.

Day 5: Infusion of glucose, intravenous to calculate the splay (renal tubular reabsorption as a function of load presented to the tubule). Inulin and endogenous creatinine clearances to be done in conjunction with the glucose infusion.

Day 6: Day of rest.

Renal Glycosuria - Fariss

Day 7: Tolbutamide tolerance test (1.0 gm I.V.) specimens for glucose and insulin at 0, 2, 15, 30, 45, 60, 90, 120, 150, and 180 minutes.

Day 8, 9, and 10: NH/Cl loading p.o. with measurement of hydrogen secretory capacity, net acidification and ammonia production each day.

PROGRESS

(79 10 - 80 09) Data collected thus far have been analyzed and fail to show any correlation of insulin and glucose responses for two individuals who have developed diabetes in comparison to those who have not developed diabetes. The mean response of insulin to a glucose load is elevated more than in a group of normal individuals.

STATUS: (0)

TITLE: The Effects of Chronic Hyperglycemia on Pregnancies and Fetuses in Sheep During Gestation

PRINCIPAL INVESTIGATOR: COL Bruce L. Fariss, MC

PROFESSIONAL ASSISTANTS: LTC Paul B. Jennings, VC
MAJ George S. Ward, VC

WORK UNIT NO: 74/06

TECHNICAL OBJECTIVE

The objectives of this project are to determine the effect of hyperglycemia upon pregnancies as manifested by frequency of abortions and hydramnios and possible developmental abnormalities of the fetuses.

METHOD

The study will be composed of three groups of pregnant ewes with as close proximity of the date of conception as possible. All groups will be given food and water ad lib.

1. The control group will be comprised of six animals with no treatment.
2. Group #2 will be composed of seven animals which have undergone subtotal pancreatectomy. The diabetes mellitus produced surgically will be managed by the injection of intermediate acting insulin such as NPH. Blood sugars will be monitored frequently as indicated clinically.
3. The third group will be composed of seven animals which have indwelling catheters for infusion of hypertonic sugar solutions with a lambda infusion system. The systems are portable, weighing less than 3 lbs and can be strapped to the backs of the animals without difficulty. Blood sugars will be monitored at frequent intervals with an attempt to keep blood sugars between 200 and 300 mg/100 ml of blood at all times.

The course of the pregnancies will be observed for each group of animals. Blood sugars for each group will be determined at frequent intervals during the gestation. At delivery the neonate will be examined pathologically for evidence of pulmonary, liver, pancreatic, kidney, and possible developmental abnormalities.

The Effects of Chronic Hyperglycemia - Fariss

PROGRESS

(79 10 - 80 09) This is an ongoing protocol. As a side line, serum zinc levels have been studied and found to be increased in animals following total pancreatectomy or ligation of the pancreatic duct in contrast to normal animals.

A paper entitled "The Effect of Total Pancreatectomy, Pancreatic Duct, Ligation, and the Administration of Alloxan on Serum Zinc Levels in Sheep" has been submitted to the American Journal of Physiology: Gastrointestinal and Liver Physiology.

STATUS: (0)

TITLE: Adrenal Hyperplasia in Pacific Salmon

PRINCIPAL INVESTIGATOR: COL Bruce L. Fariss, MC

PROFESSIONAL ASSISTANTS: LTC Stephen Plymate, MC
John DeCota

WORK UNIT NO: 80/01

TECHNICAL OBJECTIVE

To determine if the administration of a salt-retaining hormone, desoxycorticosterone, will prevent adrenal gland hyperplasia in the Pacific salmon and to determine if the Pacific salmon can spawn and survive.

METHOD

It is proposed that a total of 20 Pacific salmon be captured while in salt water. These fish are to be sexually mature and will be retained in holding pens. Half of the fish will be treated with desoxycorticosterone in oil, intramuscularly. Blood samples will be obtained from the fish for the measurement of plasma hydroxycorticosteroid, desoxycorticosterone, and aldosterone. Following the administration of the desoxycorticosterone, all of the fish (treated and controls) will be placed in a holding tank until spawning occurs. Following spawning, the fish will be returned to the holding pen in the salt water for follow-up observations of survival.

PROGRESS

(79 11 - 80 09) This protocol will be implemented in the near future. Arrangements have been made for the collection of the fish.

STATUS: (0)

TITLE: Evaluation of the Cyclic Nature of Human Semen Content

PRINCIPAL INVESTIGATOR: CPT Willis H. Jacob, MSC

PROFESSIONAL ASSISTANTS: CPT Michael L. Smith, MSC
Robert Modarelli, M.D., LTC, MC (Ret)

WORK UNIT NO: 78/34

TECHNICAL OBJECTIVE

To determine semen quality by measuring sperm count, sperm motility, sperm morphology, and various constituents of seminal fluid. These findings will then be analyzed for cyclic patterns.

METHOD

1. Test Subjects: Twenty to thirty healthy volunteers will be selected from the 9th Infantry Division or the 62nd Medical Group. Selection will be based on physical examination and medical history. Individuals will be excluded from the project for any of the following reasons: evidence of active venereal disease; a history of testicular varicocele; currently using the sauna on a regular basis; currently taking any medication; any adverse finding during the physical examination. Volunteers will abstain from the use of alcohol and other drugs throughout the semen collection phase of the project. Volunteers will abstain from sexual intercourse for a period beginning 48 hours before collection of the first semen sample and extending throughout the sample collection period.

2. Semen Collection and Analysis: Semen samples will be collected daily for a period of 20 to 25 days. Samples will be collected during a specified 30-minute period each day. The semen, obtained through masturbation, will be ejaculated directly into plastic containers which are free of trace metals. The samples will be allowed to liquefy for one hour at room temperature (240°C). The liquefied samples will be measured for volume and color, and then will be divided into two portions. One portion will be assayed immediately for viscosity, sperm count, sperm motility, and sperm morphology. The other portion of the samples will be centrifuged and the sperm-free seminal fluid will be retained for assay of seminal fluid constituents to include prostaglandins, gonadotropins, trace metals, and carbohydrates.

Evaluation of the Cyclic Nature of Human Semen Content - Jacob

PROGRESS

(79 10 - 80 19) Twelve men have completed this study and six more are scheduled to enter the study shortly. Data collected so far suggest that wide daily variations in sperm density, semen volume, and total count occur with an individual, but there is no apparent cyclicity in these variations.

STATUS: (0)

PRESENTATION: Jacob, W.H., Smith, M.L., Plymate, S.R., and Cricco, C.F.: Daily Variations in Human Semen Quality. Presented at the Pacific Coast Fertility Society Annual Meeting, October 1979.

TITLE: Correlation of the Effects of Semen Sperm Count and Prostaglandin Content on Fertility in Human Males

PRINCIPAL INVESTIGATOR: MAJ Willis H. Jacob, MSC

PROFESSIONAL ASSISTANTS: CPT Michael L. Smith, MSC
MAJ Jeffrey S. Rakoff, MC
Robert Modarelli, M.D., LTC, MC (Ret)

WORK UNIT NO: 78/45

TECHNICAL OBJECTIVE

To compare the semen quality of men of known fertility to that of men who are apparently infertile. The parameters of semen quality will be sperm count, sperm motility, sperm morphology, sperm viability, seminal prostaglandins, seminal fructose, seminal zinc, seminal gonadotropins, and gonadal steroids. Seminal prostaglandin content will be compared with each of these parameters.

METHOD

Semen specimens will be collected from 20-25 volunteers of known fertility and from 20-25 volunteers with apparent infertility. Following a urological evaluation, each volunteer will be asked to provide three semen specimens. Each volunteer will provide a semen specimen following a 48-hour period of abstinence from sexual activity. Subsequent samples, obtained at the end of a 48-hour abstinence period, will be given at one-week intervals for a two-week period. Each volunteer will ejaculate directly into a plastic container which is free of trace metals. The specimens will be analyzed for volume, color, sperm count, sperm motility, sperm morphology, prostaglandins E, prostaglandins F, and various other seminal fluid components such as fructose, zinc, gonadotropins, and gonadal steroids.

PROGRESS

(79 10 - 80 09) Efforts to recruit more volunteers are continuing. Approximately 50% of the desired number of expectant fathers have completed the study.

STATUS: (0)

Correlation of the Effects of Semen Sperm Count and Prostaglandin Content on Fertility in Human Males - Jacob

PUBLICATION:

Fariss, B.L., Fenner, D.K., Plymate, S.R., Brannen, G.E., Jacob, W.H., and Thomason, A.M.: Seminal Characteristics in the Presence of a Varicocele Compared to Expectant Fathers and Pre-Vasectomy Individuals. Accepted by Fertility and Sterility.

TITLE: Incidence of Hypothermia in Diabetic Ketoacidosis

PRINCIPAL INVESTIGATOR: LTC Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: CPT Martin Bassett, MC
Lisa Plymate, M.D.

WORK UNIT NO: 79/56

TECHNICAL OBJECTIVE

To determine the incidence, severity, and predisposing factors contributing to the development of hypothermia in diabetic ketoacidosis.

METHOD

Patients at both Virginia Mason Hospital, Seattle, WA, and Madigan Army Medical Center will be utilized, producing a subject population of approximately 50 DKA cases.

Investigators will be notified of all admissions with a diagnosis of DKA within 24 hours. In cases of hypothermia, clinical evaluation for any other underlying causes including recording of ambient temperatures during the time the patient developed symptoms and on arrival to the hospital; history of cold exposure; drug and alcohol history; presence of sepsis or metabolic disturbances potentially accounting for the state.

The procedure outlined below will be followed:

1. Monitoring of accurate temperatures with the use of a hypothermic thermometer hourly on all patients admitted in DKA over a one-year period.
2. Clinical assessment of these patients in regard to the factors contributing to their hypothermia.
3. Correlation of hypothermia with both biochemical and clinical parameters monitored during the treatment of DKA.
4. Descriptive and statistical analysis of the data thus obtained.
5. All data collection will be from histories and lab procedures that are done routinely in the treatment of DKA.

Incidence of Hypothermia - Plymate

PROGRESS

(79 10 - 80 09) This project has been completed and a paper and a presentation are now being prepared.

STATUS: (C)

TITLE: Effects of Prolactin on Seminiferous Tubule Function

PRINCIPAL INVESTIGATOR: LTC Stephen R. Plymate, MC

PROFESSIONAL ASSISTANT: MAJ George S. Ward, VC

WORK UNIT NO: 79/69

TECHNICAL OBJECTIVE

Both high and low prolactin levels have been shown to influence sperm production. Since no human model is available for studying both of these situations in the same individual, the purpose of this protocol is to evaluate the effects of high and low dose prolactin on seminiferous tubule function of the male rat.

METHOD

Thirty male post-pubertal rats are to be studied with 10 rats in each group. Photoperiod will be maintained at 14 h light and 10 h dark. Baseline testicular biopsy for morphology, testosterone, dihydrotestosterone, and androgen binding protein will be done along with serum testosterone, dihydrotestosterone, prolactin, LH, FSH, and estradiol. Ten adult rats will then be placed on 2-bromo- α -ergocryptine, 120 mg subcutaneous in oil q.d.; ten will be given cimetidine, 1mg subcutaneously b.i.d.; and ten will be given saline subcutaneously q.d. and used as controls. After six weeks the animals will be rebiopsied and serum drawn for the previously mentioned studies. After six weeks rest, the treatment groups will be switched with the first group that was on bromocriptine being put on cimetidine and those that were on cimetidine being put on bromocriptine. Prior to being remedicated, blood will again be drawn and biopsies performed. Plasma testosterone, DHT, and androgen binding protein will be measured by the method of Plymate, et al; LH, FSH, and prolactin will be measured by rat RIA NIAMMD materials.

PROGRESS

(79 10 - 80 09) This project has been completed. Laboratory data have been collected and an abstract will be submitted for presentation to the Endocrine Society Annual Meeting.

STATUS: (C)

TITLE: Sex Steroid Binding Globulin as a Marker of Excess Androgen Activity in Infertile Females

PRINCIPAL INVESTIGATOR: LTC Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
LTC Richard P. Belts, MC
LTC K. David McCowen, MC
Louis A. Matej, MT

WORK UNIT NO: 80/11

OBJECTIVE

To determine if a decrease in sex steroid binding protein can be used as a marker of excess androgen production and if this decrease (in sex steroid binding protein) in obese patients may be a cause of infertility in the obese female.

METHOD

One hundred (100) females presenting to the Infertility Clinic without male or tubal factors will have LH, FSH, estradiol, testosterone, and sex steroid binding globulin measured by radioimmunoassay. Sex steroid binding globulins will be performed by the charcoal absorption method as previously documented by Plymate, et al, in a paper presented to the Pacific Coast Fertility Society, October 1979. A history will be compiled and a physical examination will be performed, examining for parity ovulation, and hirsutism. Data will be analyzed by non-paired, one-tailed t testing and linear regression analysis.

PROGRESS

(80 02 - 80 09) This project has been completed. An abstract has been accepted for presentation at the Pacific Coast Fertility Society, October 1980, and a paper has been tentatively accepted by the Journal of Clinical Endocrinology and Metabolism.

STATUS: (C)

TITLE: Effects of Exogenous Iodine on the I^{123} Uptake of Patients with Hyperthyroidism and an Elevated I^{123} Uptake

PRINCIPAL INVESTIGATOR: LTC Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Stanton Brown, MC
COL Bruce L. Fariss, MC
LTC K. David McCowen, MC
MAJ Martin L. Bassett, MC
CPT Robert Chadband, MC

WORK UNIT NO: 80/12

OBJECTIVE

To determine if exogenous iodine can be a cause of depressed iodine uptake in patients with classic, that is high, iodine uptake type hyperthyroidism.

METHOD

Ten patients with hyperthyroidism as documented by elevated T^4 , T^3 RIA, and FTI levels with I^{123} uptakes above the upper limit of normal (25% at 24 hours) will have total serum iodine and 24 hour urinary iodine measurements performed. When these samples are collected, the patients will be given 500 μ gm of iodine a day as SSKI for 10 days and the I^{123} uptakes, serum T^4 , T^3 RIA, and free thyroxin index measurements and the 24 hour urinary iodine measurements will be repeated. SSKI has been used for short term treatment of patients with hyperthyroidism, and the use of this drug in treatment of these patients would therefore not be experimental. The administration of SSKI will delay definitive treatment of the hyperthyroidism for at least 10 days if the patient requests surgery. If I^{131} treatment is requested, there will be a delay of definitive treatment of three weeks. During this time, propranolol will be used for symptomatic control. The Student's t Test will be used for data analysis.

PROGRESS

(80 03 - 80 09) The investigators are in the process of collecting subjects. None have been available to date.

STATUS: (0)

TITLE: Effects of Testosterone and Estrogen Administration on Endorphin and Enkephalin Release in the Human Female

PRINCIPAL INVESTIGATOR: LTC Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC
CPT Allan F. Avbel, MC

WORK UNIT NO: 80/69

OBJECTIVE

To determine if women with polycystic ovary disease syndrome have an abnormal or dichotomous response in the release of endorphin and enkephalin and if this response is mediated by the gonadal steroids.

METHOD

Five women with normal weight and normal ovulation, as determined by basal body temperature, histories, and/or progesterone levels during the luteal phase of the menstrual cycle, will be given 25 mg of testosterone propionate IM in the early follicular phase of the cycle (within the first three days after cessation of menstruation) and will again be given testosterone propionate, 25 mg IM, during the mid-luteal phase which will be counted as days 21 to 23 following the onset of menstruation. Three blood samples will be drawn 15 minutes apart on the day before and the day after administration of the testosterone propionate. Samples will be assayed for LH, FSH, progesterone, testosterone, β -lipotropin, and β -endorphin. Data analysis will be by Student's t test.

PROGRESS

(80 08 - 80 09) The investigators are in the process of collecting subjects. No subjects have been available to date.

STATUS: (0)

TITLE: Mechanism of HCG in Spermatogenesis During Testosterone Suppression

PRINCIPAL INVESTIGATOR: LTC Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce Fariss, MC
MAJ George Ward, VC
Mina Garrison, MT
Louis Matej, MT

WORK UNIT NO: 80/70

OBJECTIVE

To determine if, during testosterone suppression, spermatogenesis which is reinitiated by HCG is due only to a rise in testicular testosterone or does HCG also stimulate androgen binding protein production.

METHOD

Three groups of male rats greater than 90 days old with 20 rats in each group will be studied. Initially each animal will have serum drawn for LH, prolactin, FSH, and testosterone, and a unilateral orchectomy will be done on each animal with the testicular contents assayed for androgen binding protein, testosterone, estradiol, and dihydrotestosterone plus histology. For six weeks, Group I (control group) will be injected with sesame oil alone. Groups 2 and 3 will be injected with testosterone propionate and sesame oil at a dose of 150 μ gm/100 gm body weight. Then, for six more weeks both groups will continue to receive the testosterone propionate and group 3 will also receive HCG at a dose of 6 units per 100 gram body weight daily. Group I will continue to receive the sesame oil alone. At the end of this six week period, each animal will again have serum drawn for prolactin, FSH, LH, and testosterone, and the animal will then be sacrificed with the other testicle removed and assayed for androgen binding protein, testosterone, estradiol, and dihydrotestosterone as well as histology.

PROGRESS

(80 08 - 80 09) The first six-week phase of this study has been completed. The investigators have initiated the second six-week phase of the study.

STATUS: (0)

TITLE: Semen Steroid and Protein Levels in Fertile and Infertile Males

PRINCIPAL INVESTIGATOR: CPT Michael L. Smith, MSC

PROFESSIONAL ASSISTANTS: LTC Stephen R. Plymate, MC
MAJ Willis Jacob, MSC
MAJ Wijdan A. Luqman, MC
MAJ Jeffery S. Rakoff, MC
James Graves, MT
Mina Garrison, MT
Louis Matej, MT

WORK UNIT NO: 79/72

TECHNICAL OBJECTIVE

To measure the levels of testosterone, dihydrotestosterone, prolactin, LH, FSH, and androgen binding protein in the semen of fertile and infertile men. Semen components which differ between the two groups will be noted. Correlations between components will also be studied.

METHOD

1. Patients: Fertile - 25 prevasectomy patients who have had a child within the past year. Infertile - 50 who have had no children after one year of unprotected intercourse and whose wives meet the following criteria: (a) patent tubes and (b) regular ovulatory menstrual cycles.

2. Two semen samples will be collected from 25 prevasectomy patients prior to vasectomy. One sample will be collected after vasectomy. Three semen samples will be collected from 50 infertile males. Blood samples will also be taken from all patients on the same day that semen is collected. All semen samples for the infertile patients and the postvasectomy samples are part of a routine evaluation. Seminal plasma and serum will be frozen until assayed.

3. Testosterone and dihydrotestosterone levels will be measured on all serum and seminal plasma samples using thin layer chromatography for separation and radioimmunoassay for final analysis.

4. Seminal plasma levels of androgen binding protein will be measured by a ^3H -DHT-polyacrylamide gel method developed by Dr. Plymate. Serum levels of sex binding globulin will be measured by a similar method.

Semen Steroid and Protein Levels in Fertile and Infertile
Males - Smith

5. Prolactin, LH, and FSH levels will be measured by a radioimmunoassay method using a kit furnished by the National Institute of Arthritis, Metabolism, and Digestive Diseases, Bethesda, MD. Prolactin will also be measured by a radioceptor assay using the method of Kennan, et al.

6. After all levels are measured, comparison and statistical analysis will be carried out.

PROGRESS

(79 10 - 80 09) Prolactin and luteinizing hormone (LH) were found in semen. Their concentrations correlated significantly with several parameters of fertility. The accessory sex organs contribute most of the prolactin and about a half of the immunoreactive LH to seminal plasma. Semen and seminal plasma contain three molecular sizes of prolactin. In addition, stored semen contains another unique size of prolactin not found in seminal plasma. The identity and origin of this species is unknown. No further work is planned on this protocol due to the reassignment of the principal investigator.

STATUS: (C)

PUBLICATIONS:

1. Luqman, W.A., Matej, L.A., and Smith, M.L.: Comparison of Prolactin Levels in Human Semen and Seminal Plasma. *J Endocrinol* 81:131, 1979.
2. Luqman, W.A. and Smith, M.L.: Seminal Radioimmunoreactive Prolactin Before and After Vasectomy. *Clin Endocrinol* 10:213, 1979.

Semen Steroid and Protein Levels in Fertile and Infertile
Males - Smith

3. Smith, M.L., Luqman, W.A., and Rakoff, J.S.: Correlations Between Semen Radioimmunoreactive Prolactin, Sperm Count, and Sperm Motility in Prevasectomy and Infertility Clinic Patients. *Fertil Steril* 32:312, 1979.
4. Luqman, W.A., Smith, M.L., Plymate, S.R., and Jacob, W.H.: Inherent Ranges of Seminal Prolactin in Pre and Postvasectomy Subjects. *Int J Fertil* 24:286, 1979.
5. Luqman, W.A. and Smith, M.L.: The Effect of Freezing and Storage on Seminal Immunoreactive Prolactin. *J Endocrinol Invest*, in press, 1980.
6. Smith, M.L., Luqman, W.A., and Fariss, B.L.: Size Heterogeneity of Immunoreactive Prolactin in Stored Semen and Seminal Plasma. Submitted to *Arch Androl*, 1980.

PRESENTATIONS:

1. Smith, M.L. and Luqman, W.A.: A Correlation Between Semen Prolactin Levels and Sperm Count. Annual Meeting of the Association for the Advancement of Science, 5 Jan 79, Houston, Texas, Abstract #313.
2. Luqman, W.A., Smith, M.L., Plymate, S.R., and Jacob, W.H.: Inherent Ranges of Seminal Prolactin in Pre and Postvasectomy Subjects. *Endocrinology '79*, 7th Biennial International Conference, July 1979, London, England. (Abstract)

ABSTRACTS:

Smith, M.L. and Luqman, W.A.: Seminal Immunoreactive Luteinizing Hormone Before and After Vasectomy. *Clin Chem* 27:1068, 1980.

TITLE: In vivo Uptake of $^{131}\text{I}^-$ by Semen and Other Body Fluids

PRINCIPAL INVESTIGATOR: CPT Michael L. Smith, MSC

PROFESSIONAL ASSTS: COL Bruce Fariss, MC
COL S. Brown, MC
MAJ Willis Jacob, MSC
James Graves, DAC
CPT Allan Avbel, MC

WORK UNIT NO: 80/44

TECHNICAL OBJECTIVE

To investigate the in vivo uptake of $^{131}\text{I}^-$ by human semen and to compare this to the uptake in other body fluids. Also, the effects of this $^{131}\text{I}^-$ on spermatogenesis will be investigated.

METHOD

Twelve hyperthyroid men and 6 men with thyroid cancer receiving $^{131}\text{I}^-$ for partial or complete thyroid ablation will be selected for study. Semen, blood, saliva, perspiration, and a 24-hour urine will be collected from these patients at various intervals following dosing. The first patient will be used to determine these intervals. This patient will give samples at 1,3,6,14 and 80 day(s) post-dosing then the intervals will be adjusted for the other patients to obtain a reasonable activity-time plot for each type of body fluid. Semen will be collected by having the patients masturbate and ejaculate into a polypropylene specimen container. After liquefaction, one ml will be counted in a gamma scintillation counter and a routine semen analysis will be done. 5cc of blood will be drawn into an EDTA tube: $^{131}\text{I}^-$ activity will be determined in one ml of whole blood and one ml of plasma. Saliva will be collected by having the patient chew wax, then expectorate into a polypropylene container. $^{131}\text{I}^-$ activity will be determined in one ml. Sweat will be collected utilizing pilocarpine for stimulation. 24 hour urine will be collected in 3L plastic bottles. $^{131}\text{I}^-$ activity in 2 ml will be determined. After data is collected the distribution of $^{131}\text{I}^-$ in body fluids at various periods after oral dosings will be assessed and an activity time plot will be constructed for each patient. Changes in semen analysis will also be determined. The sperm will be separated from the seminal plasma with differential radioactive counts being performed in an attempt to learn whether the iodide is bound to the sperm.

In Vivo Uptake of $^{131}\text{I}^-$ by Semen and Other Body Fluids - Smith

PROGRESS

(80 05 - 80 09) A literature review and most of the method protocols have been completed. No patients have consented to join the project at present.

Due to the departure of CPT Smith, CPT Allan Avbel, MC, will assume the role of principal investigator at the end of FY 80.

STATUS: (0)

TITLE: Development of Teaching Models for Microvascular Anastomosis, Microneural Reconstruction and Tissue Reimplantation

PRINCIPAL INVESTIGATOR: MAJ George S. Ward, VC

PROFESSIONAL ASSISTANT: None

WORK UNIT NO: 78/11

TECHNICAL OBJECTIVE

To develop teaching models for instruction and perfection of residents or staff in the field of microsurgery.

METHOD

Different species of laboratory animals and anatomical areas will be evaluated to determine which offer the least technical difficulties. Those models which are most successful will then be perfected for end to end and end to side arterial anastomosis. If interest and demand continue, models for microneural reconstruction and tissue reimplantation will also be developed. Various steps will be documented with photography. Contrast radiography will be used to demonstrate vascular patency.

The models developed under this protocol will be used to familiarize residents or other personnel with microsurgical techniques or to refresh staff proficiency prior to clinical application.

PROGRESS

(79 10 - 80 09) Microsurgery procedures have been done on 26 guinea pigs, 41 rats, 8 hamsters, and 2 rabbits. An exhibit was presented at the Annual Meeting of the American Academy of Otolaryngology, 1980. This exhibit consisted of a video tape carotid artery end-to-end anastomosis done on a guinea pig and still photographs of a double end-to-side arterial anastomosis, a vein anastomosis, and miscellaneous technique photographs.

STATUS: (0)

Development of Teaching Models for Microvascular Anastomosis,
Microneural Reconstruction, and Tissue Reimplantation - Ward

PRESENTATION:

Wells, J.R., Ward, G.S., Eckland, D., Jackson, S., and Hays, L.L.: Opportunities in Microvascular Anastomosis: A Self-Instructional Method. Annual Meeting of the American Academy of Otolaryngology, 28 Sep - 2 Oct 80, Anaheim, California. Scientific Exhibit #SE-27.

ABSTRACT:

IBID, Otolaryngology, Head and Neck Surgery 88:214, 1980.

TITLE: Level of Anesthetic Gases in Local Veterinary Operating Rooms

PRINCIPAL INVESTIGATOR: MAJ George S. Ward, VC

PROFESSIONAL ASSISTANTS: CPT Michael L. Smith, MSC
CPT Robert R. Byland, MSC

WORK UNIT NO: 79/11

TECHNICAL OBJECTIVE

To determine the level of exposure to anesthetic gases by operating room personnel in local veterinary hospitals and to evaluate the efficacy of waste anesthetic gas scavenging systems in use.

METHOD

Levles of halothane or metophane during scheduled operations under normal conditions will be monitored. If a scavenging system is present, levels will be monitored during its usage and after it is discontinued to determine effectiveness. A Milan Infrared Portable General Purpose Gas Analyzer will be used. If levels of anesthetic gases are consistently too low to be accurately determined by the Milan Gas Analyzer, gas chromatography will be utilized.

PROGRESS

(79 10 - 80 09) All data has been gathered and is in the process of being analyzed. A paper will be written within the next few months.

STATUS: (O)

TITLE: Xyladrol Evaluation in the Primate (*Macaca nemestrina*)

PRINCIPAL INVESTIGATOR: MAJ George S. Ward, VC

PROFESSIONAL ASSISTANTS: LTC Stephen R. Plymate, MC

WORK UNIT NO: 79/93

TECHNICAL OBJECTIVE

To determine if Xyladrol, an investigative veterinary pre-anesthetic/anesthetic agent, is potentially addictive, utilizing a morphine addicted pig-tailed macaque as a test animal, and to determine if any toxicity is evidenced at a continuous clinical usage rate.

METHOD

Phase 1: One monkey will be addicted to morphine and spontaneous withdrawal signs will be noted. Decreasing alleviating doses may be administered as necessary. This phase will allow observing personnel to become familiar with the ten signs of the morphine abstinence syndrome and determination of the dosage of morphine for addiction in the *Macaca nemestrina*. During this phase, a chart will be constructed to grade the degree of withdrawal symptoms.

Phase 2: Six monkeys will be addicted to morphine by the rapid addiction method at a level determined in Phase 1. The maintenance level will probably approach 12-15 mg/kg, which will be given in divided intramuscular doses BID. Substitution for morphine will then be attempted with three test substances. Xyladrol (the formulation utilized throughout this study will be 15 mg xylazine and 5 mg etoxadrol per milliliter) will be administered at the following levels: 0.025; 0.05; 0.1; 0.2; and 0.4 ml/kg. Codeine will be administered in two trials each at: 3, 6, and 12 mg/kg. Saline will be the placebo treatment. Morphine antagonistic effect will also be determined. Three test substances will be used; Xyladrol and saline at the same doses as above, and Levallophan tartrate (Lorfan-Roche) at 0.05; 0.1 and 0.3 mg/kg. A scoring card or chart will be kept on each monkey for each trial. At least one day on normal morphine maintenance will separate each trial. Menstrual cycles will be monitored and levels of estrogen, FSH, and LH will be determined weekly. LH-RH will be administered at various stages of addiction. The morphine substitution and antagonistic study is required to satisfy FDA suggestions for data to be submitted by development companies. Following the study, addicted monkeys will be gradually weaned by decreasing doses of morphine.

Xyladrol Evaluation in the Primate - Ward

Phase 3: Six different monkeys will be given a clinical dosage of Xyladrol for a period of 21 consecutive days. Clinical signs and evidence of neurological changes or addiction will be noted. Serum chemistries (SMAC) will be done at days 0, 2, 4, 6, 13, and 21. Complete blood counts will be done on days 0, 4, 13, 18, and 21. Urinalysis will be done on days 0, 7, 14, and 21. Ophthalmologic examinations will be done on days 0, 7, 14, and 21. Body weights will be recorded weekly. Menstrual cycles will be monitored and serum estrogen, FSH, and LH will be determined weekly. If changes are noted in any parameters, these will be followed every 14 days for 2-3 months or return to normalcy in 3 monkeys. The other 3 monkeys will continue Xyladrol treatment at increasing doses similar to the rapid morphine addiction schedule to determine if addiction develops. Complete histopathology will be performed on any animal that might expire.

PROGRESS

(79 10 - 80 09) The acute injection phase has been completed. The data has been collected and is being analyzed. A paper is being prepared on the technical aspect of the project.

STATUS: (0)

TITLE: Conjunctival Biopsy in the Diagnosis of Sarcoidosis

PRINCIPAL INVESTIGATOR: CPT Leslie P. Fox, MC

PROFESSIONAL ASSISTANTS: COL Stanley Sollie, MC
LTC Stanley Allison, MC
MAJ Jerome Beekman, MC
MAJ Bruce Bellin, MC
MAJ Henry Covelli, MC
MAJ Barry Weled, MC
CPT Myron Whitehead, MC

WORK UNIT NO: 79/85

TECHNICAL OBJECTIVE

To evaluate the usefulness of conjunctival biopsy as a primary means of diagnosing sarcoidosis.

METHOD

Patients with a tentative diagnosis of sarcoidosis based on accepted clinical, radiologic, and biochemical criteria will have baseline evaluations to include chest x-ray, PPD and anergy battery, angiotension converting enzyme level, erythrocyte sedimentation rate, arterial blood gases, and pulmonary function tests to assess disease activity. These patients will undergo slit lamp examination. Patients with conjunctival follicles will have those follicles biopsied and those with normal appearing conjunctiva will have random biopsies. Tissue will be examined histologically for noncaseating epithelioid granulomata with hematoxylin and eosin stain. If granulomata are observed, the specimen will be examined utilizing polarized light microscopy and stained and examined for acid fast bacilli and fungi. If no granulomata are observed, no further examination will be done. Patients will then be evaluated with transbronchial lung biopsy. If the diagnosis is not established by this method, further invasive diagnostic procedures will not be done unless deemed necessary for the management of the patient. Data on the field from transbronchial biopsy will be compared to that from conjunctival biopsy. In addition, disease activity as manifest by serum ACE level will be correlated with biopsy positivity.

Conjunctival Biopsy in the Diagnosis of Sarcoidosis - Fox

PROGRESS

(79 10 - 80 09) Data has been gathered on approximately 20 patients. Work continues on the project; however, data gathering has become more difficult since this technique has become a standard of care.

Due to the departure of CPT Fox, MAJ Henry Covelli has assumed the duties as principal investigator of this protocol.

STATUS: (O)

TITLE: The Use of Fluoride and Custom Trays to Treat Dental Hypersensitivity Away From the Dental Office

PRINCIPAL INVESTIGATOR: MAJ Robert Collins, DC

PROFESSIONAL ASSISTANTS: MAJ Kjeld Hansen, C.A.F.
MAJ Lloyd Dixon, DC
LTC Richard Falonski, DC

WORK UNIT NO: 78/19

TECHNICAL OBJECTIVE

To determine the effectiveness of the utilization of custom trays and a fluoride gel to eliminate or decrease dental hypersensitivity, especially after periodontal surgery, and to evaluate this method for possible future self-treatment by the patient.

METHOD

Patients who have dental hypersensitivity after periodontal treatment will be screened to reflect surgery in opposite quadrants, either the maxilla or mandible. The patient's base pain threshold will be measured using a thermo-electric tooth stimulator, invented by Dr. M. Ash of the University of Michigan, giving a baseline to measure from. The patient will have a custom tray (made of acrylic) fabricated to his specific oral anatomy of the teeth. Using the custom tray, dental personnel will apply a fluoride gel (strength 2.3%) to the tested site once a day for five minutes. The patient will be measured reference hypersensitivity and verbally questioned every week for one month. A 15 member group using a placebo and the above method will be used as a control. The findings will be accumulated and placed in a graphic/table form for analysis.

PROGRESS

(79 10 - 80 09) Construction of the power source for the thermo-electric tooth stimulator was completed in FY 79. However, the project had to be terminated due to a lack of subjects as well as insufficient time for the investigator to complete the project before reassignment.

STATUS: (T)

TITLE: Vital Root Retention Below the Height of the Maxillary Alveolous

PRINCIPAL INVESTIGATOR: MAJ Clinton C. Guiry, DC

PROFESSIONAL ASSISTANTS: COL Robert Todd, DC
LTC Michael Krakow, DC
MAJ Leslie Alexander, VC
Murray Bartley, D.D.S., Univ of Oregon

WORK UNIT NO: 79/86

TECHNICAL OBJECTIVE

Evaluation of the retained vital root below the crest of the alveolar process to determine if there is any osteogenic activity over the retained root and to evaluate the contents of the pulp tissue to determine if true vitality of the retained root is maintained.

METHOD

The maxillary right canine tooth will be reduced 5 millimeters below the height of the alveolar bone in 6 one-year old beagle dogs. A mucoperiosteal flap will be reflected before the tooth is reduced and will undergo primary closure with 5-0 chromic gut. The dogs will be put on a soft diet for 5 days, then changed to normal diets. Healing will be monitored on a weekly basis, visually and radiographically for the first 2 months and then bi-weekly for 8 months. A block of six retained roots will be taken and submitted for histologic evaluation.

PROGRESS

(79 10 - 80 09) The study is completed and a manuscript has been submitted for publication. Histologic evidence indicates greater biocompatibility in the submerging of vital versus endodontically treated teeth. The problem of chronic inflammation which has plagued so many of the studies using endodontically treated teeth was not in evidence in any of the test animals. There were, however, intrapulpal changes which cannot, without further research, be accepted as normal. Furthermore, despite the formation of mature bone over the submerged root, it cannot be assumed that similar results would be achieved if the test teeth were stressed by the placement of prostheses.

STATUS: (C)

TITLE: A Clinical Determination of the Effectiveness of Endodontic Chemomechanical Sterilization

PRINCIPAL INVESTIGATOR: COL David R. Zielke, DC

PROFESSIONAL ASSISTANTS: COL John W. Harrison, DC
LTC John P. Heggars, MSC (Ret)

WORK UNIT NO: 75/22

TECHNICAL OBJECTIVE

To evaluate the efficacy of an accepted root canal preparation technique in producing sterilization of the root canal system.

METHOD

The plan is to endodontically treat single-rooted asymptomatic teeth that have roentgenographic evidence of periapical pathosis. All teeth will be isolated with a rubber dam and a conventional access preparation made. Two microbiological samples from each canal system will be made prior to instrumentation and at the completion of instrumentation. One will be incubated in pre-reduced sterilized medium and the other in trypticase soy broth with 0.1% agar as the control. Canal preparation will now be completed in a conventional manner.

At each subsequent appointment, two additional microbiological samples will be obtained before and after instrumentation. All canals will be obturated by the lateral condensation of gutta percha and sealer.

The patients will be reexamined at 6 and 12 month intervals. Another roentgenograph will be made. They will be placed in success or failure categories as defined by Storms. The findings will be correlated with the culture results.

PROGRESS

(79 10 - 80 09) A total of 244 paired samples were obtained from 61 root canal systems at four specific stages of endodontic treatment. Half the samples were placed in a commonly used endodontic medium and incubated aerobically. The remaining samples were placed in PRS medium and incubated in an anaerobic environment. The rereduction procedure, used to remove oxygen entering the PRS medium at the time of insertion of the sample, was not employed. A statistical analysis of the results indicates that the non-rereduced PRS medium is not

A Clinical Determination of the Effectiveness of Endodontic Chemomechanical Sterilization - Zielke

as sensitive as rereduced PRS and offers no significant advantages over trypticase soy broth with 0.1% agar.

The technical portion of this protocol is completed, and has resulted in two publications. A third paper is planned from the remaining data.

STATUS: (C)

PUBLICATIONS: Zielke, D.R., Heggers, J.P., and Harrison, J.W.: A Statistical Analysis of Anaerobic vs Aerobic Culturing in Endodontic Therapy. *Oral Surg Oral Med Oral Path* 42:830-837, 1976.

Zielke, D.R., Heggers, J.P., and Harrison, J.W.: An Analysis of the Sensitivity of Non-Rereduced PRS Medium in Endodontic Therapy. *Oral Surg Oral Med Oral Path* 47:83-86, 1979.

TITLE: Hydrocarbon Induced Changes in Lung Tissue After GI Absorption

PRINCIPAL INVESTIGATOR: CPT William H. Dice, MC

PROFESSIONAL ASSISTANTS: LTC James Kelley, MC
MAJ William Kilpatrick, MC
MAJ George Ward, VC
1LT Joseph High, MSC

WORK UNIT NO: 80/75

TECHNICAL OBJECTIVE

To determine if pulmonary damage can result from gastrointestinal absorption of hydrocarbons.

METHOD

Esophageal transection and placement of a gastrostomy will be performed on 12 healthy dogs. Control radiographs will be taken before surgery. After allowing for an adequate period for recovery of GI function, evidenced by a return to normal bowel movements, an LD₅₀ dose of kerosene will be instilled in all gastrostomies. At 24 hr post installation, one half of the animals will be sacrificed following radiologic exam of the lungs. The other one half will have radiographs at 24, 48, and 72 hr. Sacrifice will occur after 72 hr radiographs have been obtained. Autopsies will be performed, and the tissue preserved for light microscopic examination of the brain, major organs, and gastrointestinal tract.

PROGRESS

(80 09 - 80 09) This protocol has only been approved for two weeks. Assemblage of equipment and scheduling of dogs is being done.

STATUS: (0)

TITLE: Local Anesthesia in Minor Wounds, Topical TAC versus Lidocaine Infiltration

PRINCIPAL INVESTIGATOR: CPT Gary J. Pryor, MC

PROFESSIONAL ASSISTANTS: MAJ William Kilpatrick, MC
CPT Duane Opp, ANC

WORK UNIT NO: 80/18

TECHNICAL OBJECTIVE

To evaluate the incidence of wound complication, ease and speed of surgical repair, and patient acceptability of topical TAC vs lidocaine infiltration.

METHOD

A total of 150 patients will be randomly evaluated. After standard wound preparation and saline flush, even numbered patients (by last four digits of social security number) will have the wound infiltrated with lidocaine 1% with epinephrine. Odd numbered patients will receive 5 cc of TAC per 3 cm applied topically to the wound with a folded 2x2 eye patch which will be left in place for 10 minutes. The wound will then be debrided and sutured as appropriate. The physician will then fill out a questionnaire as to patient affect, size of wound, and wound check at 48-72 hours for infection, hematoma, abscess, and dehiscence.

PROGRESS

(80 02 - 80 09) This study is completed. One hundred and fifty (150) patients were treated with either topical TAC or subcutaneous lidocaine with similar results for anesthetic efficacy, wound complication rates, etc.

A manuscript has been accepted for publication.

STATUS: (C)

PRESENTATION: University Associates/Emergency Medicine Annual Conference, Tucson, Arizona, April 1980;
Pryor, G.J., Kilpatrick, W.R., and Opp, D.R.:
Local Anesthesia in Minor Lacerations: Topical TAC vs Lidocaine.

TITLE: Emergency Room Procedure Training

PRINCIPAL INVESTIGATOR: MAJ Robert D. Smith, MC

PROFESSIONAL ASSISTANTS: MAJ Wilson R. Kilpatrick, MC
MAJ George S. Ward, VC

WORK UNIT NO: 80/04

TECHNICAL OBJECTIVE

To provide training to acquire the necessary manipulative skills in performing invasive, life-saving procedures for the Emergency Medicine Residency Program.

METHOD

After a lecture with visual demonstration of the procedures, in an initial session each resident will be assigned a large anesthetized dog. Under staff supervision the following procedures will be performed: venous cutdown; peritoneal lavage; cricothyreotomy; trachcostomy; chest tube insertion; lateral thoractomy; cross clamping aorta; and cardiac wound repair. Six month after the initial session, the residents will repeat the procedures and will be timed for each procedure to simulate emergency conditions and to evaluate how effective the initial training has been.

PROGRESS

(79 11 - 80 09) Six Emergency Medicine residents have been trained in techniques of multiple emergency procedures during the past year. A manuscript is in preparation.

Due to the departure of MAJ Smith, MAJ Wilson Kilpatrick has assumed the duties of the principal investigator.

STATUS: (0)

TITLE: Children in the E.R., Whose Patients?

PRINCIPAL INVESTIGATOR: LTC Matthew J. Walsh, MC

PROFESSIONAL ASSISTANTS: COL Errol Alden, MC
LTC James F. Bascom, MC

WORK UNIT NO: 80/74

TECHNICAL OBJECTIVE

To determine the reason for visits to the ER by children.

METHOD

Records from the ER were reviewed for a 12-month period with consideration being made for the reason the child was being seen.

PROGRESS

(80 09 - 80 09) All records have been reviewed. There were a total of 61,006 visits with 33% being pediatric ER visits. Twenty-five per cent of the patients were under the age of 5. Less than 2% of the children were admitted to the hospital while these admissions from the ER accounted for 25% of all admissions to the pediatric ward. It was found that 40% of these patients were seen for trauma, surgical problems, and poisonings, with the remainder having a large range of diagnoses. Reviews of pediatric emergency visits at other centers in the area are consistent with this analysis. The pediatric age patient comprises a significant proportion of patients seen in the ER. Pediatric and Emergency Medicine Residents will be exposed to this environment after training. Optimal teaching demands adequate utilization and care of these patients in all training programs.

A paper has been accepted for presentation at the Golden Anniversary Annual Meeting of the American Academy of Pediatrics, October 1980 in Detroit, Michigan.

STATUS: (C)

TITLE: Severity of Illness in After-Hours E.R. Visits:
The Physician's Assessment versus the Patient's

PRINCIPAL INVESTIGATOR: CPT Robert E. Stuart, MC

PROFESSIONAL ASSISTANT: CPT Joseph Divita, MC

WORK UNIT NO: 80/59

TECHNICAL OBJECTIVE

To compare the patient's estimation of the urgency/severity of his medical problem with the physician's assessment in after-hours emergency visits and to gather information about what kind of services after-hours patients expect.

METHOD

Patients presenting between 1700 and 0800 weekdays and on a 24-hour basis on weekends will be included for a period of two weeks. At the time of the patient's visit, the physician will place a code number on the chart as follows: (1) true emergency; (2) acute or chronic severe illness; (3) acute minor illness; (4) chronic minor illness; and (5) no illness found. The patient will be asked to complete a questionnaire at the time he presents for treatment as to his opinion of his illness as categorized above and if he thought he was presenting to the ER or an after-hours walk-in clinic. Later, a telephone survey of patients will be done by an assistant who does not have access to the code, asking patients to categorize their opinion of their illness after seeing the physician.

PROGRESS

(80 07 - 80 09) Recent changes in triage procedure and personnel necessitated reworking the questionnaires. Data collection is scheduled to begin within the month. A computer data collection system to be instituted in the next few weeks will simplify examination of outcomes.

STATUS: (0)

TITLE: **Compliance and Efficacy in Administration of Oral Cephalosporins in an Outpatient Setting**

PRINCIPAL INVESTIGATOR: CPT Arden L. Ashton, MC

PROFESSIONAL ASST: MAJ John McClain, MC
CPT Hyrum Blackburn, MC

WORK UNIT NO: 80/35

TECHNICAL OBJECTIVE

To compare two different administration schedules of cephalosporins in the treatment of urinary and skin and skin structure infections.

METHOD

Patients reporting to the Outpatient Clinic will be randomized into group A, who will receive Cefadroxil, 1000 mg po qd for 7 days, and group B, who will receive Cephapirin, 250 mg po qid for 7 days. An additional two day supply of pills will be given as extra pills. The patients will have a clinical follow-up at 10 days when pill count will be done and evaluation of the underlying infection is made. Efficacy will be analyzed by chi square. Compliance will be analyzed by considering all patients who forgot to take one or more pills during therapy by chi square. A second analysis will correlate number of pills omitted with chance of treatment failure. One hundred patients will be treated in each group.

PROGRESS

(80 03 - 80 09) To date, 65 patients have been evaluated for the study. Because of the design of the study, a fraction of those patients have been entered presumptively before culture results are back based on clinical findings. Only 16 of 65 patients turned out to have urinary infections as defined by greater than 100,000 bacteria/ml of urine. This is too low and the protocol design is being redone. The failure rate in both groups seems to be the same.

Due to the departure of CPT Ashton, CPT Blackburn will assume the responsibilities as principal investigator on this protocol.

STATUS: (0)

TITLE: The Relationship of Improving Diabetic Control by Home Monitoring of Blood Glucose to Hemoglobin A_{1C} Measurements and Leukocyte Chemotaxis, Phagocytosis, and Intracellular Killing in Diabetic Patients

PRINCIPAL INVESTIGATOR: MAJ Martin Bassett, MC

PROFESSIONAL ASSISTANTS: LTC David McCowen, MC
MAJ Martin Crumrine, MSC
CPT Allan Avbel, MC

WORK UNIT NO: 79/55

TECHNICAL OBJECTIVE

To demonstrate that chemotaxis, phagocytosis, and intracellular killing by polymorphonuclear leukocytes in diabetic patients can be normalized and maintained by optimum control of blood glucose levels.

METHOD

Fifteen patients with poor blood glucose control who have had no previous insulin therapy or are poorly controlled on their present regimen and are non-acidotic will be asked to participate. Fifteen healthy volunteers, age matched, without diabetes, cancer, current infection, recent surgery, or having taken any medications for two weeks will be selected to act as controls for the leukocyte function studies.

Blood glucose will be monitored by home use of an Ames "Eyetone" meter and Dextrostix measurements (6 times/day) until stable and then maintaining tight control by weekly measurement of hemoglobin A_{1C}. Insulin dosage will be adjusted using twice daily dosages of regular and NPH insulin to closely approximate fasting blood sugars between 80 and 120 mg%.

When the patients are hospitalized for control of their diabetes, they will be instructed in the use of the Dextrostix and the Eyetone meter and in the recording of blood sugar, urine sugar and acetone, caloric intake, and activity, along with instruction in insulin use, diet, etc. A regimen of regular and NPH insulin in the mornings and evenings will be used. Upon return to the home, approximately one week will be needed to "fine tune" the control and stabilize the insulin dosage. Thereafter, when a patient begins to slip from control, he/she will be reissued the home monitoring kit for various periods of time to maintain control.

The Relationship of Improving Diabetic Control - Bassett

Leukocyte Function Tests: Whole heparinized blood will be drawn at the beginning of hospitalization, between 2 and 4 weeks after control, and again 2-4 months after control is achieved, and evaluated along with appropriate control samples.

Hemoglobin A_{1C}: Hemoglobin A_{1C} will be checked at the beginning of hospitalization and then weekly during the study with concomitant fasting blood sugars and fasting urine sugar and acetone values to check against the patient's chart of home obtained values and to monitor the overall control over a period of approximately 4-6 months.

PROGRESS

(79 10 - 80 09) The hemoglobin A_{1C} assay technique has been completed and tested. However, chemotaxis, phagocytosis, and killing assays have not been perfected. Dr. Bassett has been transferred to Letterman Army Medical Center and will submit a similar protocol there. CPT Allan Avbel will continue the work on this protocol at Madigan as the principal investigator.

STATUS: (0)

TITLE: Serum High Density Lipoprotein Concentrations in Non
Insulin-Dependent Diabetes Mellitus

PRINCIPAL INVESTIGATOR: MAJ Martin L. Bassett, MC

PROFESSIONAL ASSTS: Robert Biesbroeck, M.D., Univ of Washington
COL Bruce Fariss, MC
LTC K. David McCowen, MC
MAJ Wijdan Luqman, MC
CPT Robert Chadband, MC

WORK UNIT NO: 80/09

TECHNICAL OBJECTIVE

The purpose of this joint protocol with the University of Washington is to evaluate HDL levels in stable, untreated, non-insulin dependent adult diabetics. This study will provide important baseline data on HDL concentrations in this diabetic population. Hemoglobin A_{1c} levels will also be determined and compared with the baseline HDL levels. Hemoglobin A_{1c} is presently thought to reflect the chronic state of overall control of blood glucose values in the diabetic. It will be of significant interest to compare the H A_{1c} levels with the HDL value to assess the effect of the degree of hyperglycemia on HDL cholesterol. These substances will also be compared to triglycerides, cholesterol, blood sugar, insulin, and other lipoproteins.

METHOD

Approximately 50 adult type II diabetic patients on no oral hypoglycemic medication will be studied. The patients will be asked to come to the Endocrine Clinic after an overnight fast on two different mornings approximately 60 days apart. They will have 30 cc of blood drawn, give a urine specimen, and complete a questionnaire designed to assess the patient's diabetic stability. Blood analyses will be done by the University of Washington under Dr. Biesbroeck's direction.

PROGRESS

(80 02 - 80 09) The technical portion of this protocol has been completed. The serum specimens are currently being processed at the University of Washington. A paper is planned when data analysis is complete.

STATUS: (0)

TITLE: The Acute Effects of Water Loading and Deprivation
on ADH Levels on Two Patients with Essential
Hypernatremia

PRINCIPAL INVESTIGATOR: MAJ Martin L. Bassett, MC

PROFESSIONAL ASSTS: CPT Robert Chadband, MC
LTC Stephen R. Plymate, MC
COL Bruce L. Fariss, MC
LTC K. David McCowen, MC

WORK UNIT NO: 80/10

TECHNICAL OBJECTIVE

To determine the response of plasma ADH to water loading and water deprivation in two patients with essential hypernatremia.

METHOD

Two patients will be admitted to the hospital for a two day stay.

Day 1 - Water load: After an overnight (12 hr) fast without fluids, each patient will have an indwelling IV catheter inserted with D₅W solution running. Blood samples will be removed, after flushing the catheter, every hour (15-20 cc's) to measure plasma ADH, serum Na⁺, plasma osmolality, and serum glucose. Approximately 4-5 hours and up to 100 cc's of blood will be needed for this phase. During the test, oral water will be given at a dosage of 20 cc/kg of body weight and supplemental D₅W added to lower the serum Na⁺ to approximately 145 mEq/dl. The theoretical consideration of cerebral edema will be watched for with vital signs, mental status checks, and observation every 30 min at a minimum. Urine osmolality will be checked hourly and urine volume and body weight recorded.

Day 2 - Water deprivation: After a normal breakfast and fluid ad lib during the previous night, no fluids will be given for approximately 8 hours. The indwelling IV line will be in place from the previous day. Baseline blood samples will be drawn for the same measurements as on Day 1 through the flushed IV line until urine osmolality changes less than 30 mg/hr or until 3% of body weight is lost. At that point, 5 units of aqueous vasopressin (ADH) will be given IM and the same samples obtained one hour later. Urine osmolality and body weight will be measured hourly. This test will take approximately 8 hours and 200 cc's of blood to complete. As on Day 1, patients will be monitored every 30 minutes.

The Acute Effects of Water Loading and Deprivation on ADH
Levels on Two Patients with Essentail Hypernatremia - Bassett

Osmolalities, serum sodiuns, and vasopressins will be compared
during the water loading and water deprivation studies.
Patterns will be evaluated, if present, and comparisons made
with accepted normal values.

PROGRESS

(80 05 - 80 09) The plasma ADH samples have been collected
on one patient. The other patient is now an Oregon resident
and will not be able to complete the study. The samples
that have been obtained will be assayed and data analyzed when
funds become available.

STATUS (0)

TITLE: Study of Daily and/or Diurnal Variation in Angiotensin Converting Enzyme

PRINCIPAL INVESTIGATOR: LTC Jerome F. Beekman, MC

PROFESSIONAL ASSISTANTS: MAJ Barry J. Weled, MC
MAJ Henry D. Covelli, MC

WORK UNIT NO: 79/63

TECHNICAL OBJECTIVE

To study a group of patients with sarcoidosis and controls to determine whether a daily variation or diurnal variation in serum angiotensin converting enzyme is present.

METHOD

Ten patients with sarcoidosis and 10 controls (20-50 years of age who do not have any disease known to be associated with elevated angiotensin converting enzymes) will have specimens drawn twice a day, once in the morning and once in the afternoon, for five consecutive days, and the results will be analyzed. An assay for ACE tests will be developed at the Department of Clinical Investigation and will be used in this project.

PROGRESS

(79 10-80 09) This project was terminated due to difficulties in developing the ACE assay and reassignment of staff involved in the development of the assay.

STATUS: (T)

TITLE: Diagnostic Utility of CSF Serologies and Rabbit Inoculation in Neurosyphilis

PRINCIPAL INVESTIGATOR: CPT Cornelius P. Brooke, MC

PROFESSIONAL ASSISTANTS: LTC John K. Podgore, MC
CPT Shannon M. Harrison, MC

WORK UNIT NO: 77/93

TECHNICAL OBJECTIVE

To evaluate the diagnostic utility of cerebrospinal fluid VDRL, FTA, FTA-absorbed, and rabbit testicular inoculation with dark-field microscopic examination in the diagnosis of neurosyphilis.

The second purpose of this project is to determine if adequate cerebrospinal fluid levels of penicillin can be achieved on an outpatient treatment schedule.

METHOD

Twenty patients will be chosen in whom syphilis of more than one year's duration is suspected. After physical exam, LP will be performed for fluid for animal culture, cell count, glucose, protein, VDRL, and FTA-ABS and FTA-unABS. CSF (0.5 cc) will be injected into the testis of a young male rabbit with a control negative VDRL. Evidence of a positive culture will be taken by darkfield microscopy as demonstration of treponema in the injected testicle and not the control testicle.

One-half of the patients will be randomly selected for treatment with 2.4×10^6 units benzathine pen IM q. week x 3 as the CDC recommends and retapped 24 hours after the third dose. Penicillin levels will be measured and recorded. If the initial LP was positive for treponema, repeat injection will be carried out with a CSF specimen from three weeks post-treatment.

One-half of the patients will be treated with 1.2×10^6 units procaine pen IM q. day x 10 days. Repeat LP will be done 4 hours after tenth dose for a measurement of the penicillin levels. If the initial LP was positive for treponema, repeat injection will be carried out with a specimen from three weeks post-treatment.

Diagnostic Utility of CSF Serologies and Rabbit Inoculation
in Neurosyphilis - Brooke

PROGRESS

(79 10 - 80 09) Ten attempts were made to isolate the spirochetes from eight patients with positive serologies. This organism was not demonstrated at any time following a repeat inoculation.

STATUS: (C)

TITLE: The Clinical Evaluation of Naloxone (NARCAN) as a Diagnostic Agent in the Differential Diagnosis of Hyperprolactinemia.

PRINCIPAL INVESTIGATOR: CPT Robert Chadband, MC

PROFESSIONAL ASSISTANTS: COL Bruce Fariss, MC
LTC Stephen Plymate, MC

WORK UNIT NO: 80/15

TECHNICAL OBJECTIVE

To determine if, by comparing the results of the prolactin response to bromocryptine and Narcan, a separation can be made between pituitary hypersecretors and hypothalamic hyperstimulators.

METHOD

To be eligible, patients must have had two prolactins >20 ng/ml by RIA. Twenty-five patients will be evaluated. One week after the standard evaluation for hyperprolactinemia, baseline prolactins will be drawn and then at 5, 30, 60, and 120 minutes. Narcan, 0.8 mg IV, will then be given thru heparin lock. Phlebotomy of 10cc will again be done at 0, 15, 30, 60, 90, 120, 150, and 180 minutes. 5cc will be spun and sent for prolactin analysis. The following week, patients will be given 2.5 mg bromocryptine PO and phlebotomy will again be performed as before. After completion of these tests, patients will be treated in accordance with standard medical care for the suspected cause of hyperprolactinemia. Patients will be followed on a monthly basis for at least 6 months. After collection of the raw data, results will be analyzed using Student's t Test and linear regression analysis.

PROGRESS

(80 08 - 80 09) Final paperwork has been completed with the FDA and the project will begin shortly.

STATUS: (0)

TITLE: Comparison of Ipecac and Gastric Lavage in Removal of Stomach Contents in the Treatment of Toxic Ingestion

PRINCIPAL INVESTIGATOR: CPT Robert Chadband, MC

PROFESSIONAL ASSTS: COL Bruce L. Fariss, MC
LTC James Bascom, MC
COL Joel Sim, MC

WORK UNIT NO: 80/16

TECHNICAL OBJECTIVE

To study the comparative benefit of emesis and gastric lavage in the treatment of acute toxic ingestion.

METHOD

Twenty-five patients will be admitted in sequence with toxic ingestion of solid materials (pills). The patients to be studied will be between 18-40 years old who have no recognized contraindications to Ipecac/emesis (allergy, corrosives, petroleum products, decreased sensorium, or absent gag reflex). 15 cc of Ipecac will be given PO. Emesis will be continued until clear (the standard endpoint of therapy). Patients will be placed on their left side and an Ewald tube will be placed PO and the stomach contents lavaged with normal saline with 250-500 cc minimum. Gross observation will be made on aspirate for food or pill particles.

PROGRESS

(80 04 - 80 09) Patients are being studied in the Emergency Room and data is being collected. Data will be analyzed when a sufficient number of subjects has been studied.

STATUS: (0)

TITLE: To Determine if Tolinase (Tolazamide) Exerts Clinically Detectable β Adrenergic Stimulatory Effects in AODM Patients without Known ASCAD

PRINCIPAL INVESTIGATOR: CPT Robert Chadband, MC

PROFESSIONAL ASSTS: COL Bruce Fariss, MC
LTC Theodore Steudel, MC

WORK UNIT NO: 80/17

TECHNICAL OBJECTIVE

To determine which patients may or may not be suitable for the use of oral hypoglycemic agents and to determine if there is a possible risk of β stimulatory effects on AODM patients without known ASCAD.

METHOD

Ten patients, who have no allergy to the medication and no known symptomatic ischemic cardiac disease by history, physical, or baseline ECG and who would normally be considered as candidates for oral agents will initially receive 250 mg Tolinase while continuing on appropriate diabetic diet. All patients will have a baseline ECG followed by Holter monitor and graded Bruce Treadmill Test (BTM). Patients developing ischemic symptoms on BTM will be withdrawn and treated appropriately. Initial fasting and 2hPP glucoses will be done and records of urine reductions will be recorded. Tolinase dosage will be increased at one week intervals as necessary to obtain a 2hPP glucose < 250 mg% and followed for a total of 3 months with fasting and 2hPP glucoses to the maximal dose of 750 mg/day. Blood levels of oral agents will be drawn after one week on stabilizing dose and before BTM. Patients will be withdrawn from the study with decompensation, DKA, or ischemic coronary symptoms.

Ten patients who are age matched AODM, sex matched, and on diet therapy will be used as controls.

All patients will be asked to record any palpitation or cardiac symptoms and will be followed at one month intervals as outpatients.

TO Determine if Tolinase (Tolazamide) Exerts Clinically Detectable β Adrenergic Stimulatory Effects in AODM Patients Without Known ASCAD - Chadbard

PROGRESS

(80 04 - 80 09) The investigators are in the process of selecting patients for the study.

STATUS: (0)

TITLE: Treatment of Rheumatoid Arthritis with Oral Zinc Sulphate

PRINCIPAL INVESTIGATOR: LTC Sidney Cloud, MC

PROFESSIONAL ASSISTANTS: COL Robert B. Gibbons, MC
MAJ Michael D. Herring, MC

WORK UNIT NO: 79/12

TECHNICAL OBJECTIVE

To determine whether changes in serum zinc levels and/or serum histidine levels will correlate with improvements of arthritic symptoms or with occurrence of side effects in patients with rheumatoid arthritis taking oral zinc sulfate.

METHOD

Patients with rheumatoid arthritis who have been taking oral zinc sulfate will be studied at monthly intervals with evaluation of disease activity accomplished by patient assessment and measurement of grip strength, enumeration of joints with active disease and by sedimentation rate. Blood for zinc and histidine will be drawn at monthly intervals. These subjects will be followed long-term and the investigators will continue to correlate activity of disease with zinc and histidine levels. Statistical analysis of data will compare zinc and histidine with the recorded variables of the disease.

PROGRESS

(79 10 - 80 09) The patient evaluation and clinical trial of oral zinc sulphate with or without the addition of histidine have been completed. The evaluation of serum levels of zinc and histidine has been completed and the analysis of data is continuing. It appears that there is no difference in either clinical course of the disease or in serum levels of zinc and/or histidine between the patient receiving zinc sulphate alone and those receiving zinc sulphate plus histidine.

STATUS: (0)

TITLE: Distribution of Gold Used to Treat Rats with Adjuvant Arthritis

PRINCIPAL INVESTIGATOR: LTC R. Sidney Cloud, MC

PROFESSIONAL ASSISTANTS: MAJ George S. Ward, VC

WORK UNIT NO: 79/13

TECHNICAL OBJECTIVE

To determine the distribution of gold salts injected in rats with adjuvant arthritis and to correlate distribution with effect on the arthritis.

METHOD

Adult male rats will be given gold by injection or by mouth. Disseminated arthritis will be produced by the injection of Freund's adjuvant. The animals will be sacrificed at 4, 8, 12, and 16 days and tissue surveyed for gold concentration. Clinically, the degree of arthritis will be compared in the control versus the treated animals.

PROGRESS

(79 10 - 80 09) The initial phase of the study has been completed with the rats having been injected with adjuvant and various controlled substances and treated with two different doses of intramuscular gold. Statistical analysis of the difference in arthritis among the various groups is in progress. Techniques for the determination of gold by atomic absorption are being developed.

STATUS: (0)

TITLE: Distribution of Gold in Tissues of Patients Being Treated with Gold Salts for Arthritis

PRINCIPAL INVESTIGATOR: LTC R. Sidney Cloud, MC

PROFESSIONAL ASSISTANTS: COL Robert B. Gibbons, MC
MAJ Michael D. Herring, MC

WORK UNIT NO: 79/14

TECHNICAL OBJECTIVE

To measure levels of gold concentration in various tissues in patients being treated with gold for arthritis and to correlate the development of toxicity and response to therapy with these tissue levels.

METHOD

Subjects will be divided into three groups. Group 1 will be patients receiving gold as current standard treatment who will be studied to establish ranges of gold levels that can occur in tissues during gold therapy. As these patients will not have had objective measurement of disease taken prior to gold, correlation of gold levels and disease will not be possible, but correlation of gold tissue levels with total dose of gold given will be done. Group 2 will be ten patients currently on gold therapy for rheumatoid arthritis. Group 3 will be ten patients not currently on gold but in whom gold therapy is to be started. All patients will continue to receive standard medical treatment.

All groups will have gold levels in lymphocytes, PMN's, RBC's, and urine measured every three months. Gold levels in synovium, lymph nodes, and other tissues will be done on samples acquired at time of any surgery done as part of normal medical care. Clinical studies will be done on Groups 2 and 3. Grip strength, number of affected joints, duration of morning stiffness, and ring size of PIP's will be recorded every three months. Group 3 will have additional gold levels in blood and urine measured at the first and second months. Gold levels will be determined by atomic absorption spectrophotometry. Separation of blood cells will be done by density gradient techniques.

Distribution of Gold in Tissues of Patients Being Treated
with Gold Salts for Arthritis - Cloud

PROGRESS

(79 10 - 80 05) Technical problems with gold analysis were encountered with this study. Also, this study has already been done by other investigators for two years on a much larger scale and in more detail than is possible at MAMC. Therefore, it has been terminated.

STATUS: (T)

TITLE: Study of the Effect of d-Penicillamine and Chloroquine on Antigen and Mitogen-Induced Human Lymphocyte Proliferation

PRINCIPAL INVESTIGATOR: LTC R. Sidney Cloud, MC

PROFESSIONAL ASST: MAJ Martin Crumrine, MSC

WORK UNIT NO: 80/43

TECHNICAL OBJECTIVE

To determine if d-penicillamine and/or chloroquine inhibit lymphocyte transformation induced by antigens and mitogens in treatment.

METHOD

Human peripheral blood mononuclear cells (PBM) from 10 normal volunteers will be stimulated in tissue culture by the addition of concanavalin A (Con A), pokeweed mitogen (PWM), phytohemagglutinin (PHA) and streptokinase-streptodornase (SKSD). The culture will be done in triplicate in microtiter plate.

Initially the effect of d-penicillamine (d-Pen) and chloroquine (AM) added to the cultures prior to stimulation will be studied. The amount of DNA synthesis will be measured by incorporation of tritiated thymidine (3HT). The time of optimum effect will be established by assaying 3HT uptake daily from the second through the sixth day. The length of culture producing optimum inhibition will be used in the remaining investigation.

The effect of varying concentration of d-Pen and AM will be studied against optimal and suboptimal concentrations of Con A and PHA.

The effect of adding d-Pen and AM at different times in the cycle of stimulation will be done with the agents added at time of stimulation and at 1, 2, 4, and 48 hours post stimulation. To determine whether the lymphocytes are injured so they can not be stimulated, PBM will be cultured with Con A for 24 hours and then washed to remove Con A. These cells will then be cultured for 48 hours with and without the inhibiting

Study of the Effect of d-Penicillamine and Chloroquine on
Antigen and Mitogen-Induced Human Lymphocyte Proliferation -
Clouda

drugs. Another way to study this effect will be to culture PBM with the inhibiting agents for 5 days, wash the cells, and continue culture for 48 hours in fresh media with the mitogens and with or without fresh autologous monocytes. Additional studies on the role of monocytes will be done by reducing the number of monocytes in the cultures.

Cell death will be evaluated by trypan blue exclusion and cell counts. Possible formation of suppressor cells will be evaluated by adding preincubated monocytes to stimulated cultures containing normal monocytes.

Data will be analyzed using the paired t test and χ^2 analysis to compare stimulated to non-stimulated values and the response of treated vs untreated controls.

PROGRESS

(80 05 - 80 09) The necessary agents and supplies have been obtained and work on this project has recently started.

STATUS: (0)

TITLE: Study of the Effects of Drug Treatment in Rheumatoid Arthritis: I. The Effect of *in vivo* Gold Injection on Mononuclear Cell Stimulation *in vitro*.

PRINCIPAL INVESTIGATOR: LTC R. Sidney Cloud, MC

PROFESSIONAL ASST: MAJ Martin Crumrine

WORK UNIT NO: 80/46

TECHNICAL OBJECTIVE

To determine if gold acts *in vivo* to inhibit mononuclear cell function as measured by response to mitogens *in vitro*. The relationships of frequency of injection and dose will be correlated with effect on lymphoblastic transformation by mitogens.

METHOD

Twenty patients receiving gold injections for RA will be studied. Controls will be 20 patients with RA not receiving gold, antimalarials, penicillamine, or immunosuppressive drugs. Patients will be grouped for analysis according to frequency of gold injections and dose of gold injected.

Venous blood will be collected just prior to injection of gold and 24-48 hours after (a minimum of two and a maximum of three times with each patient). Clinical data to include duration of disease, laboratory data on disease, activity in ESR, latex fixation for RF, ANA, and estimation of benefit of therapy by the patient and by the physician will be correlated with the results. Patient controls will have two samples of blood drawn approximately one month apart.

PBM will be separated from the blood by standard ficoll separation techniques and cultured in triplicate in microtiter plates. Phytohemagglutinin, pokeweed mitogen, concanavalin A or streptokinase/streptodornase will be used to stimulate the cells. Incorporation of tritiated thymidine into DNA of peripheral blood mononuclear cells (PBM) on the third day of culture will be measured in stimulated and non-stimulated cells. Gold levels in the PBM will be measured by atomic absorption. Student's t test and chi square analysis will be performed on the data to compare the study and control populations.

Study of The Effects of Drug Treatment in Rheumatoid Arthritis:
I. The Effect of *in vivo* Gold Injection on Monocuclear Cell
Stimulation *in vitro* - Cloud.

PROGRESS

(80 06 - 80 09) The necessary agents and supplies have arrived and work on this project has just begun.

STATUS: (0)

AD-A100 955

MADIGAN ARMY MEDICAL CENTER TACOMA WASH
CLINICAL INVESTIGATION SERVICE ANNUAL RESEARCH PROGRESS REPORT -ETC(U)
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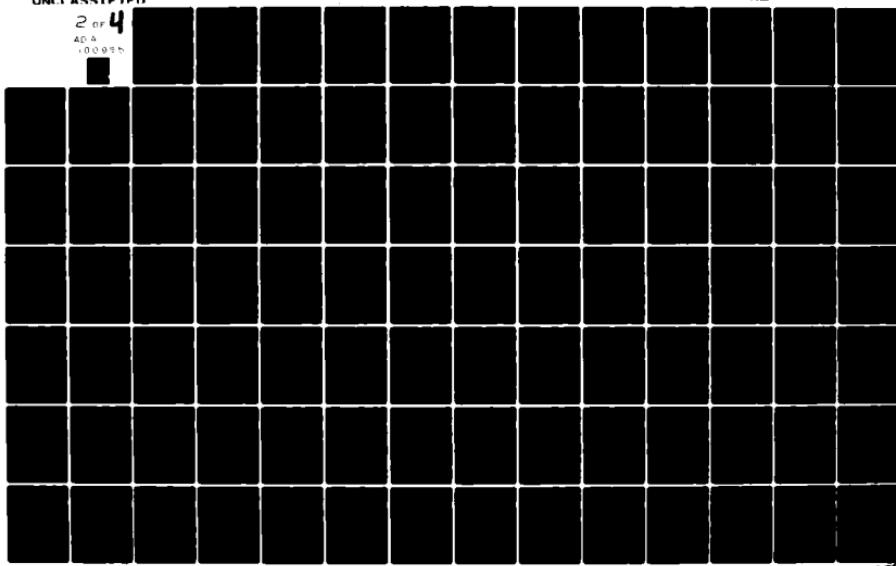
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2 of 4

AD-A
100 955



TITLE: Evaluation of Radiation Therapy in the Management of Endoscopically Visible Tumors of the Lung

PRINCIPAL INVESTIGATOR: MAJ Henry D. Covelli, MC

PROFESSIONAL ASSTS: LTC Jerome Beekman, MC
LTC Donald Kull, MC
MAJ Barry Weled, MC

WORK UNIT NO: 79/77

TECHNICAL OBJECTIVE

To evaluate in a prospective manner the utility of using radiation therapy to decrease tumor size in obstructing carcinomas of the lung.

METHOD

A minimum of 15 patients with carcinoma of the lung will be evaluated in the usual manner. If the patient is a non-operable candidate with endoscopically visible lesions, he will receive radiation therapy and/or chemotherapy in the usual manner with reassessment of pulmonary functions, arterial blood gases, and fiberoptic bronchoscopy approximately one month after radiation and again approximately six months after radiation. The parameters used to evaluate progression or regression of disease will be changing roentgenographic effect (collapse, atelectasis) in the area of involvement, alteration of pulmonary function and arterial blood gases, and changing luminal size of obstructing lesions as noted by fiberoptic bronchoscopy. Repeat biopsy results from prior areas of involvement would also be used to assess therapeutic results.

PROGRESS

(79 11 - 80 09) Twelve patients have entered the study, but only routine data have been accumulated.

STATUS: (0)

TITLE: 5-Azacytadine in Acute Leukemia

PRINCIPAL INVESTIGATOR: LTC Irwin Dabe, MC

PROFESSIONAL ASSTS: COL Friedrich Stutz, MC
MAJ Lauren Colman, MC

WORK UNIT NO: 80/19

TECHNICAL OBJECTIVE

To examine the efficacy of 5-Azacytadine in patients with acute leukemia refractory to conventional therapy.

METHOD

5 Azacytidine will be given in a dose of 300 mg/M²/day for 5 days in three or four divided doses each day. Courses will be repeated every three weeks unless there is earlier evidence of recovery from myelotoxicity. If bone marrow cellularity is less than 20% at three weeks from the last course, chemotherapy will be withheld until marrow cellularity exceeds 20%. Dosages for the next course will then be reduced by one third. If there is no improvement in the bone marrow after the initial course, the drug dosage for the second course will be increased by one third.

PROGRESS

(80 06 - 80 09) Two patients have been treated on this study:

- a. One had myelomonocytic leukemia and had been previously treated on several regimens with only a brief response to DNR/Ara-C. She received two cycles of AZA achieving a minimal response to the first (decrease in marrow blast % from 80-35) and very little response to the second (45% blasts in the marrow six weeks later). She died of uncontrolled leukemia. The only toxicity was nausea and vomiting.
- b. The other had myelomonocytic leukemia and after no response to Ara-C/BTG and DNR/Ara-C was given two cycles of AZA, achieving a good partial response after the first cycle. She died of uncontrolled CNS leukemia during marrow aplasia from the second dose.

STATUS: (0)

TITLE: Post-Synovectomy Synovial Fluid Analysis

PRINCIPAL INVESTIGATOR: COL Robert B. Gibbons, MC

PROFESSIONAL ASSISTANTS: CPT William A. Bulley, MC
CPT Kerry A. Randolph, MC
CPT William L. Clayton, MC

WORK UNIT NO: 80/05

TECHNICAL OBJECTIVE

To determine changes which occur in synovial fluid following routine, standard meniscectomy or synovectomy.

METHOD

Synovial fluid analysis will be performed in 25 consecutive patients at 5 and 10 days following standard meniscectomy or synovectomy. Results will be tabulated and compared to well established normal values.

PROGRESS

(80 02 - 80 09) This protocol is completed and a manuscript has been submitted to Arthritis and Rheumatism.

Synovial fluid from the knee joints of 20 consecutive patients following elective meniscectomy was prospectively examined. The results document a variable leukocyte response varying from 450 to 117,200 cells per cubic millimeter (mean value 8,647). The percentage of polymorphonuclear leukocytes varied from 0 to 53 with a mean value of 23%. Synovial fluid cultures were uniformly sterile in all patients regardless of the cell count. Surgical trauma may invoke dramatic synovial fluid leukocyte responses in the absence of infection.

A presentation entitled "Synovial Fluid Analysis Following Meniscectomy, A Prospective Study" has been accepted for presentation at the Present Concepts in Internal Medicine Meeting, October 1980, Letterman Army Medical Center.

STATUS: (C)

TITLE: Coronary Arteriography in the Army

PRINCIPAL INVESTIGATOR: MAJ John M. Harris, Jr., MC

PROFESSIONAL ASST: COL John Hill, MC

WORK UNIT NO: 80/60

TECHNICAL OBJECTIVE

To explore the use of coronary arteriography in Army Medicine, to evaluate certain technical aspects of the procedure, and to better define the nature of coronary artery disease in the active duty population.

METHOD

The proposed study will encompass all Army medical centers performing coronary arteriography. The proposed collection form will be distributed to the other medical centers for comments, then there will be completion of a procedure manual and trial of data collection at MAMC. After final revision of collection form, if necessary, initiation of data collection will begin at each medical center. A computer program for screening and initial display of data will be developed. At the completion of the first year of data collection the data will be analyzed for a report to the Association of Army Cardiology.

The study will be a prospective survey of current practices. All patients who undergo left heart catheterization will be included. Baseline data will be collected on all patients who undergo cardiac angiography.

PROGRESS

(80 07 - 80 09) The procedure manual has been developed, and all medical centers have been contacted and all but one will participate. The initial computer programs have been developed and debugged at MAMC. Data collection for the study was initiated the last month of FY 80.

STATUS: (0)

TITLE: I. Determination of the Effects of Chemotherapy and of Malignancy on the Nutritional Status of the Patient; II. Hyperalimentation of Nutritionally Depleted Patients to Improve Their Survival and Response to Chemotherapy

PRINCIPAL INVESTIGATOR: Suresh B. Katakkar, M.D., DAC

PROFESSIONAL ASSISTANTS: LTC Friedrich H. Stutz, MC
LTC Joel W. Black, MC
LTC Charlene P. Holt, MC
MAJ John J. Pelosi, MSC
CPT Jeannie Gallo, SP
Mary J. Oboy, R.N., DAC
Marleen Black, R.N.

WORK UNIT NO: 79/65

TECHNICAL OBJECTIVE

It has been known that chemotherapeutic drugs by causing nausea, vomiting, and anorexia do interfere with nutrition of cancer patients; however, so does the progressive malignancy. The objective is to measure objectively tumor responses or non-response and the side effects of chemotherapy and do objective measurements of nutritional status of the patients and attempt to delineate what role both chemotherapy and progressive malignancy play in causing nutritional imbalance.

Once imbalance is documented, the investigators plan to hyperaliment these patients and determine the effects on their nutritional status, tolerance of chemotherapy, and objective tumor response.

METHOD

1. All newly diagnosed cancer patients (approximately 50) will have an assessment of nutritional status as a baseline; including cell mediated immunity.
2. Patients will be classified as having adjuvant chemotherapy or chemotherapy for metastatic disease.
3. Nutritional assessment will be done every 4 weeks and cell mediated immunity will be determined every 12 weeks, unless abnormal at the beginning, on those patients who are on chemotherapy.
4. The side effects at chemotherapy will be graded according to SWOG criteria.

Determination of the Effects of Chemotherapy - Katakkar

5. The objective response of tumor will be measured every 4 weeks if the objective tumor measurement is by special procedures such as liver or bone scan, in which case they will be done every 12 weeks.

6. If the patient is nutritionally depleted and unable to take oral feeding, then only will he be hospitalized for parenteral feeding or enteral tube feeding. Hyperalimentation will be done for a period of 10-15 days. However, such an aggressive step will be taken only if the underlying malignancy has reasonable chance of response to therapy and meaningful life is judged to be left by the investigators.

PROGRESS

(79 10 - 80 09) Part I of this project has been completed, namely determining the effects of chemotherapy as well as that of malignancy on the nutritional status of the patient. The analysis of the results of this study will be completed within in the next few months. Part II to the study has not been initiated to date.

Due to the departure of Dr. Katakkar, COL Friedrich Stutz, MC, is to assume the role of principal investigator on this study.

STATUS: (0)

TITLE: Dietary Fat and Its Relation to Recurrence of Breast Cancer

PRINCIPAL INVESTIGATOR: Suresh B. Katakkan, M.D., DAC

PROFESSIONAL ASSISTANTS: LTC K. David McCowen, MC
LTC Stephen R. Plymate, MC
LTC Friedrich H. Stutz, MC
MAJ Martin L. Bassett, MC
ILT Ellen Bracy, SP

WORK UNIT NO: 79/66

TECHNICAL OBJECTIVE

To determine the role of the dietary fat through prolactin-estrogen balance for the recurrence of the breast cancer both in pre and postmenopausal patients.

METHOD

The plan is to investigate the role of dietary fat by obtaining the normal dietary patterns in high risk group and breast cancer patients (approximately 40). A diet history will be taken and a blood sample obtained to determine serum prolactin, estradiol, serum cholesterol, and triglyceride levels. These patients will be closely followed in the Oncology Clinic and an attempt will be made to correlate the fat content, prolactin-estrogen ratio, and the recurrence of breast cancer with the disease-free interval.

PROGRESS

(79 10 - 80 09) Four patients have been entered on this study. No results are available at this time because it is a long term follow-up study.

Due to the departure of Dr. Katakkan, Dr. F. R. Stutz, has assumed the role of principal investigator on this protocol.

STATUS: (0)

TITLE: Glucose Homeostasis in Pregnancy and Its Relationship to Gestation and Infant Wellbeing

PRINCIPAL INVESTIGATOR: MAJ Wijdan A. Luqman, MC

PROFESSIONAL ASSISTANTS: COL Joseph Sakakini, MC
MAJ Jeffery Rakoff, MC
CPT Walter Moore, MC
CPT Charles Saunders, MC
CPT Michael Smith, MSC
William Tuttle, Ph.D., DAC

WORK UNIT NO: 78/37

TECHNICAL OBJECTIVE

The diagnosis of diabetes has had different criteria during pregnancy. The objective of this study is to identify and analyze the risk factors and mechanisms associated with hyperglycemia and other problems of glucose metabolism during pregnancy.

METHOD

Retrospective studies will be undertaken. These will be done on clinical data obtained from patients' records, e.g., correlations between blood glucose values, birth weight, outcome of pregnancy, etc. The records utilized will be past records (2 years) available at Madigan Army Medical Center. Patients' involvement will not be required nor will patients be required to undergo any tests. Records will be reviewed by physicians involved and data analyses will be examined by statistical methods. Non-physician assistants will be involved in data analyses only. Identification of risk factors and mechanisms of disease will be analyzed by computer and statistical analysis.

PROGRESS

(79 10 - 80 09) Data were analyzed on 52 uneventful pregnancies at risk for diabetes, terminating in physiologic labor and delivery at 40 ± 2 weeks of the calculated gestation. The data suggest that birth weight correlates with third trimester indices of maternal glycemia and that fetoplacental maturation interrelates with indices of maternal glycemia.

STATUS: (C)

Glucose Homeostasis in Pregnancy and Its Relationship to
Gestation and Infant Wellbeing - Luqman

PUBLICATIONS:

1. Luqman, W.A., Saunders, C., Moore, W., Smith, M.L., and Kulwin, R.: Third Trimester Glucose Homeostasis and Feto-placental Maturation. *Amer J Obstet Gynecol* 135:550, 1979.
2. Luqman, W.A. and Smith, M.L.: Maternal Glycemia and Birth Weight. *Int J Gynecol Obstet* 18:63-65, 1980.

ABSTRACT: Maternal Glycemia and Birth Weight. Abstracts of Endocrinology '79, 7th Biennial International Conference, July 1979, London, England, p 77.

PRESENTATIONS:

1. A Fetal Weight Determinant Based on Maternal Glycemia and Positive Caloric Balance in Non-Diabetic Pregnant Women. Armed Forces District of American College of OB GYN and Armed Forces Seminar (Combined Meeting), 15 Oct 78, Washington, DC.
2. Maternal Glycemia and Birth Weight - A Spectrum not a Syndrome. Annual Meeting of the American Association for the Advancement of Science, 3 Jan 79, Houston, TX (Abstract #314).
3. Interrelations of Feto-Placental Maturation, Maternal Glycemic Indices and Birth Weight. Advanced Postgraduate Course in Hungary, Satellite Symposium to the 10th Congress of the International Diabetes Federation, 16 Sep 79, Budapest, Hungary.
4. 40th Annual Scientific Session of the American Diabetes Association. *Diabetes* 29 (suppl 2):59A, 1980.

TITLE: Dietary Habits and Birthweights

PRINCIPAL INVESTIGATOR: MAJ Wijdan A. Luqman, MC

PROFESSIONAL ASSISTANTS: COL Joseph Sakakini, MC
LTC Errol R. Alden, MC
MAJ Charles G. Saunders, MC
CPT Thomas H. Moraczewski, MC
CPT Sarah H. Smith, SP
CPT Michael L. Smith, MSC

WORK UNIT NO: 79/18

TECHNICAL OBJECTIVE

To examine the dietary habits and their relationship to birth weight in otherwise healthy uncomplicated pregnancies. Preliminary studies suggest that dietary habits are an important variable in studies pertaining to maternal glycemia and the birth weight.

METHOD

Fifty to one hundred patients with healthy uncomplicated pregnancies will be randomly selected and asked to provide a detailed dietary history. These data in conjunction with information from the patients' charts will be analyzed by statistical methods to reexamine the relationship between dietary habits and birthweight. Women with known risk factors, i.e., high blood pressure, smoking, anemia, weight gain <6 kg or >25 kg, glycosuria, proteinuria, will be excluded from the study.

PROGRESS

(79 10 - 80 09) Information on dietary habits of subjects during the third trimester of pregnancy was obtained. Data on fetal outcome were not obtained due to the reassignment of the majority of the investigators. This protocol has been terminated.

STATUS: (T)

TITLE: In vitro Studies of Seminal Fluid

PRINCIPAL INVESTIGATOR: MAJ Wijdan A. Luqman, MC

PROFESSIONAL ASSISTANTS: LTC Stephen R. Plymate, MC
MAJ Martin Crumrine, MSC
CPT Michael Smith, MSC

WORK UNIT NO: 79/67

TECHNICAL OBJECTIVE

To study the relationship of endocrine indices to male fertility in semen.

METHOD

Hormonal and biochemical indices will be measured in seminal fluid samples collected from approximately 40 patients undergoing vasectomy or attending the Infertility Clinic. A routine semen analysis will be done, including pH. The following parameters will be measured: FSH, LH, prolactin, testosterone, dihydrotestosterone, fructose, and citric acid. In addition, binding studies will be performed on spermatozoa to determine the various roles of these components in fertility. A follow-up will be done on these patients using the medical record as the source.

PROGRESS

(79 10 - 80 09) Preliminary observations have been obtained on a few samples. There is a suggestion that the addition of antibody may impair motility but the addition of prolactin did not improve hypomotile sperm.

STATUS: (C)

TITLE: Reversal of Endotoxin Produced Hypotension in the Rat

PRINCIPAL INVESTIGATOR: MAJ John B. McClain, MC

PROFESSIONAL ASSTS: MAJ Martin Crumrine, MSC
MAJ George S. Ward, VC

WORK UNIT NO: 80/13

TECHNICAL OBJECTIVE

It has been demonstrated in the rat model that naloxone, an opiate antagonist with no agonist activity, will reverse endotoxin induced hypotension and hypovolemic hypotension. This is a new and unexpected observation. The hemodynamic role of endorphin receptors is totally undefined. If these phenomena are reproducible and transferable across species lines then naloxone may prove useful in the therapy of hypotensive states in humans. The investigators will also study the effectiveness of this agent in the dose ranges where it has been used in humans with no ill effects.

METHOD

All studies will be conducted in conscious rats with chronically indwelling arterial and venous catheters. Two days prior to administration of the endotoxin, the animals will be anesthetized with phenobarb (50 mg/kg) and the carotid artery and jugular vein will be cannulated and the catheters brought out subcutaneously from the site of implantation. Arterial catheters will be connected to a transducer graph system. The venous catheter will be used for injections. On the day of experimentation, endotoxin (12 mg/kg) is given IV followed by 0.3 ml of saline flush to insure that the drug has infused. Naloxone will be given as an IV bolus to the following groups of 10 rats each: Group A - Endotoxin only; Group B - 10 mg/kg at 15 min; Group C - 10 mg/kg at 30 min; Group D - 10 mg/kg at 60 min; and Group E - 2 mg/kg at 30 min. Parameters which will be measured are: survival at the end of 30, 60, 90, and 120 minute post-endotoxin periods. Pulse and blood pressure throughout the experimental period. Survival data will be analyzed using the chi square method. Blood pressure data will be analyzed for significance with the Student's t test to compare values at a common interval from endotoxin administration.

Reversal of Endotoxin Produced Hypotension in the Rat - McClain

PROGRESS

(80 01 - 80 09) Surgery has been performed on approximately 60 animals. The investigators were unable to reproduce the hypotensive effects as reported in the original article. It is unclear why this is so. Upon arrival of KDO, a standard used in endotoxin assay, the potency of the endotoxin will be determined.

The investigators have attempted to induce hypotension via a hemorrhagic model. There has been some success; however, because of the large volume of fluid injected with naloxone, a clear-cut response vis-a-vis saline control has not been elicited. Using smaller volumes of morphine sulfate, the investigators were able to demonstrate an antihypotensive effect of morphine sulfate. The investigators feel that this is an unrecognized phenomenon and may represent a similar phenomenon as naloxone reversal of shock. Work is progressing to obtain a more concentrated solution of naloxone.

STATUS: (0)

TITLE: Susceptibility of Anaerobic Bacteria to Vancomycin

PRINCIPAL INVESTIGATOR: MAJ John McClain, MC

PROFESSIONAL ASST: MAJ Martin Crumrine, MSC

WORK UNIT NO: 80/34

TECHNICAL OBJECTIVE

To define in a quantitative manner using broth, agar, and disk methods the susceptibility of anaerobic genera to vancomycin in concentrations normally achieved in the therapy of human patients.

METHOD

Anaerobic isolates will be re-identified according to accepted methods of anaerobic identification. Organisms will be handled in gas-pak's and a glove box. Anaerobic organisms will have susceptibilities performed using broth and agar dilution techniques and disc susceptibility techniques. The glove box is to be made by the Instrumentation Department at WRAIR.

PROGRESS

(80 04 - 80 09) A glovebox has been constructed and preliminary attempts have been made to achieve anaerobic conditions with a catalysis-anaerobic atmosphere. These attempts have been unsuccessful. Further work on the protocol may have to be done using the gas-pak system.

STATUS: (0)

TITLE: The Effect of Aspirin on Blood and Urine Thyroxine in Induced Primate Hyperthyroidism

PRINCIPAL INVESTIGATOR: LTC K. David McCowen, MC

PROFESSIONAL ASSISTANTS: LTC Paul B. Jennings, VC
MAJ George S. Ward, VC

WORK UNIT NO: 77/03

TECHNICAL OBJECTIVE

To evaluate the effect of aspirin on the fate of serum and urine thyroxine in pigtail macaque monkeys.

METHOD

Eight *Macaca nemestrina* monkeys were paired and given 1.0 mg LT₄ intravenously 24 hours before receiving 1.2 mg ASA, orally, on the morning of the study. One monkey received the ASA with the other receiving only LT₄. Baseline serum T₄ levels were determined at 30 minute intervals, 2 to 4½ hours after the ASA was given, and serum ASA levels were determined at 3 hours after administration. Six weeks later, the same pair of monkeys were studied in identical fashion, with the exception that control monkeys received the ASA with the other monkey serving as the control. T₄ levels were determined by RIA in the Clinical Investigation Laboratory.

PROGRESS

(79 10 - 80 09) The animal model utilized was changed from the canine to the primate because the thyroid system of the monkey more closely parallels that of the human. Thus the title was changed from "canine hyperthyroidism" to "primate hyperthyroidism." The protocol has been completed. Results failed to establish any effect of salicylates on excretion and/or metabolism of thyroid hormone.

STATUS: (C)

TITLE: Comparison of the Protein-Sparing Modified Fast with Conventional Dietary Therapy in the Treatment of Obesity

PRINCIPAL INVESTIGATOR: LTC K. David McCowen, MC

PROFESSIONAL ASSISTANTS: COL James W. Reed, MC
MAJ Wijdan A. Luqman, MC
MAJ Edward Przasnyski, MC
CPT Robert B. Chadband, MC
CPT Nancy Cronmiller, AMSC
CPT Raymond Parker, MSC
CPT Sarah Smith, AMSC

WORK UNIT NO: 78/07

TECHNICAL OBJECTIVE

This protocol will explore the efficacy of treating obese patients with an outpatient experimental diet as compared with conventional diet therapy as currently administered by Diet Therapy at MAMC. This study will address the initial rate of weight loss, the success of chronic therapy in maintaining the achieved lower weight, the problem of loss of muscle (protein) mass resulting in fatigue and poor compliance, and the psychological variables in individuals being treated for obesity to seek ways of psychological intervention which might increase the effectiveness of the diet regime.

METHOD

Adult obese patients 30% above ideal body weight (IBW) will be identified and referred for evaluation. A complete physical examination and a biochemical screen will then be done. Patients will be randomly assigned to either the Protein-Sparing Modified Fast (PSMF) (1.5 gm/kg/IBW/day lean protein plus prenatal vitamins, one/day; Titralac tablets 2 bid; K-lyte one/day) or a conventional 1000 calorie diet. The patients will be seen by the contact physician every month for a follow-up SMAC-20 and reassessment. Five standard psychological assessment procedures will be given before the beginning of diet therapy, after weight reduction to approximately 50% of IBW, when IBW is reached, approximately three months after reaching IBW. Upon achievement of IBW, the patients will be entered on maintenance programs and followed for a period of 9 months.

Comparison of the Protein-Sparing Modified Fast with
Conventional Dietary Therapy in the Treatment of Obesity -
McCowen

PROGRESS

(79 10 - 80 09) The protocol has been completed. Early analysis establishes the efficacy of the PSMF diet in short term, but not chronic, treatment of simple obesity.

STATUS: (C)

TITLE: The Effect of Insulin Therapy on LDL Degradation and Lysosomal Enzyme Activity

PRINCIPAL INVESTIGATOR: LTC K. David McCowen, MC

PROFESSIONAL ASSISTANTS: MAJ Wijdan A. Luqman, MC
MAJ Martin L. Bassett, MC
CPT Robert B. Chadband, MC
Alan Chait, M.D., Univ of Washington

WORK UNIT NO: 80/03

TECHNICAL OBJECTIVE

Insulin dependent diabetes is well known to be associated with accelerated atherosclerotic vascular disease. The purpose of this joint protocol with the University of Washington School of Medicine is to investigate the effect of insulin therapy on certain cholesterol degradative pathways. This may provide more information about the role of the uncontrolled diabetic state in the associated accelerated atherogenesis.

METHOD

A total of ten adult patients with uncontrolled diabetes mellitus not currently receiving oral hypoglycemic agents requiring the initiation of insulin therapy will be referred to the University of Washington Clinical Research Center. Blood will be drawn before, during, and after initiation of insulin therapy to assess the effect of insulin therapy on LDL lysosomal enzyme activity including cholesterol ester hydrolase. Patients will be instructed in insulin therapy and have adjustments in insulin dosage as medically indicated. No investigational agents will be given to patients. After the initial evaluation, the patient will be discharged from the University of Washington Clinical Research Center and will be routinely followed as an outpatient at Madigan. One repeat blood sample will be drawn at the University as an outpatient one month after beginning insulin treatment.

PROGRESS

(80 01 - 80 09) Terminated because no patients were entered on the protocol and the principal investigator resigned from the Army.

STATUS: (T)

TITLE: Hormonal Changes in Patients Placed on Cimetidine for Treatment of Ulcer Disease

PRINCIPAL INVESTIGATOR: MAJ Edward J. Przasnyski, MC

PROFESSIONAL ASSISTANTS: LTC Stephen R. Plymate, MC
LTC David McCowen, MC
CPT Verle Bohman, MC

WORK UNIT NO: 79/70

TECHNICAL OBJECTIVE

To determine the effect of Cimetidine therapy on the levels of various polypeptide and steroid hormones prior to, during, and after this therapy in adults.

METHOD

Thirty male patients who have been placed on Cimetidine for therapeutic reasons will be asked to participate. Histories will be taken to include fertility, ethanol intake, use of medications, and illnesses. Basal levels of FSH, LH, testosterone, dihydrotestosterone, estradiol, and prolactin will be determined from serum. The patient will be asked to have blood drawn for these determinations again two weeks and four weeks following initiation of Cimetidine therapy and two weeks and four weeks following discontinuance of therapy. Sex steroid globulin levels will also be determined.

PROGRESS

(79 10 - 80 09) This project is completed. The studies demonstrated that cimetidine exerts its antiandrogen effect at the receptor level leaving the hypothalamic pituitary axis intact.

A paper has been accepted for presentation at the Western Society for Clinical Research Meeting in February 1981.

STATUS: (C)

TITLE: Serum Angiotensin Converting Enzyme (ACE) Levels in Thyroid Disease

PRINCIPAL INVESTIGATOR: MAJ Edward Przasnyski, MC

PROFESSIONAL ASSISTANT: MAJ Martin Bassett, MC

WORK UNIT NO: 79/71

TECHNICAL OBJECTIVE

Measurement of serum ACE levels in patients with hyperthyroidism, hypothyroidism, euthyroid goiter, and controls to determine the interrelationship between ACE and these diseases as compared to controls.

METHOD

Patients seen by the investigators in the Endocrine Clinic for evaluation of thyroid disease will have blood samples drawn for thyroid function studies as a routine part of their evaluation.

Controls will be patients seen in the Endocrine Clinic for problems other than thyroid who will have samples drawn as a routine part of their evaluations.

Statistical analysis will be undertaken to determine whether patients with thyroid dysfunction have statistically higher levels than a control group consisting of patients without thyroid disease or other diseases known to elevate ACE levels by the use of an unpaired t test.

PROGRESS

(79 10 - 80 09) This study has been completed. ACE levels were found to be elevated in 10 of 13 thyrotoxic Graves' disease patients prior to treatment (ACE, $42.35 \pm S.E.M. U/ml$). Euthyroid control values were $19.83 \pm 2.6 U/ml$. Elevated values were found to return to normal in 3 of 4 patients. The fourth patient had sarcoidosis. There was a highly significant difference between ACE levels in thyrotoxic patients and patients who were euthyroid or hypothyroid. There was a positive linear correlation between both the free thyroid index and the T_4 levels with the ACE levels in the thyrotoxic patients. Thyrotoxicosis can be added to the list of diseases associated with elevated ACE levels.

Serum Angiotensin Converting Enzyme Levels in Thyroid Disease -
Przasnyski

A paper is in preparation and will be submitted to the Annals
of Internal Medicine.

STATUS: (C)

TITLE: Daunomycin Therapy in Acute Leukemia (Phase II)

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANT: None

WORK UNIT NO: 78/04

TECHNICAL OBJECTIVE

This is not a research study, but rather a treatment protocol involving an experimental drug. The objective is to continue the use of daunomycin in combination with other conventional chemotherapeutic agents for the treatment of leukemia as an extension of Phase I of the protocol, but with a different regimen of drugs.

METHOD

Daunomycin in combination with cytosine arabinoside, 6-thioguanine, vincristine, and prednisone will be given for seven days as remission induction treatment. A bone marrow sample will be obtained in 2-4 weeks; if evidence of the leukemia persists, a second induction course will be given. If leukemia cells are visibly absent, one to two additional courses will be given as consolidation therapy in an attempt to eliminate any residual leukemic cells. At that point, maintenance therapy will be provided. Dosage and duration of therapy are outlined in paragraph 6.0 of the protocol.

PROGRESS

(79 10 - 80 09) Two patients have been treated:

1. Patient had a T-cell leukemia and was given one cycle as consolidation of complete remission achieved by vincristine and prednisone. He was transferred to another hospital within days afterward, so the ultimate outcome is not known, though he had little in the way of immediate side effects.
2. This patient had a smouldering myelomonocytic leukemia with a prior partial response to Ara-C/btg but rapid relapse. His marrow was cleared of blasts (severe hypoplasia), but he died of aspergillosis prior to marrow recovery.

STATUS: (0)

TITLE: Case Control Questionnaire for Patients with Large Bowel Cancer and Their Relatives Without It.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANT: Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 79/78

TECHNICAL OBJECTIVE

To identify and confirm factors associated with large bowel cancer. Controls are siblings of patients with large bowel cancer in order to eliminate most hereditary and cultural factors.

METHOD

All colo-rectal cancer patients at Madigan who are, in the opinion of the physician, willing and able to complete a questionnaire and have a sibling who is willing and able to do the same will be asked to complete a questionnaire including questions regarding life style, diet, family history, medical history, and the Srole Anomie Scale. Phase I will be a pilot study to include 30-50 matched pairs. After evaluation of the pilot study, Phase II will be initiated to include 500+ matched pairs of patients. There will be an annual follow-up of patients and analysis of response. Long-term follow-up is planned to determine if risk factors correlate with actual colo-rectal cancer incidence.

PROGRESS

(79 10 - 80 09) Six patients were entered by MAMC and 18 by other institutions for the pilot study. Since then the protocol has been revised and submitted for NCI funding as a SWOG study. If funding is forthcoming, the revised protocol will be submitted for approval.

STATUS: (0)

TITLE: In vitro Identification of Tumor Associated Antigens
PRINCIPAL INVESTIGATOR: COL Clarence M. Virtue, MC
PROFESSIONAL ASSISTANT: MAJ Martin H. Crumrine, MSC
WORK UNIT NO: 75/14

TECHNICAL OBJECTIVE

The purpose of this investigation is to identify, using an in vitro technique, the tumor associated antigens of breast carcinoma.

METHOD

Phase I: Ten C₃H-strain mice with implanted murine breast carcinoma will be obtained, and, after tumor growth has progressed beyond palpable stage, the mice will be sacrificed, and tumor tissue removed. Tissue treatment as listed in protocol.

Phase II: Tumor tissue obtained from the Department of Pathology (either from autopsy or surgical specimen) and non-tumor tissue from the same subject will be emulsified and treated in a similar manner as the mouse tumor tissue outlined in Phase I.

Phase III: Once the specific tumor associated antigens from mouse breast carcinoma are separated (Phase I), the antigens will be pooled and held at -80°C. Forty C₃H-strain mice with implanted murine breast carcinoma will be obtained. Ten of these mice will be separated and have no further procedures. Twenty other mice will undergo resection of the tumor mass, and ten will subsequently receive an injection of the specific murine tumor associated antigens (obtained in Phase I) combined with Fruend adjuvant, followed by a booster injection with tumor associated antigen without tumor resection. The mice will then be observed and compared.

PROGRESS

(79 10 - 80 09) Murine mammary tumor tissue extraction has been subjected to molecular separation in Sephadex G200 column. Concentrated separation segments have been given to subject mice before tumor load given and mice are now being observed for tumor growth.

STATUS: (0)

TITLE: Serum RAST Titer Changes in Allergic Patients on Desensitization and the Correlation with Skin Test Changes

PRINCIPAL INVESTIGATOR: COL Clarence M. Virtue, MC

PROFESSIONAL ASSISTANTS: LTC Joel W. Black, MC
LTC John C. Espinosa, MC

WORK UNIT NO: 77/67

TECHNICAL OBJECTIVE

To study the changes in serum IgE reagenic antibody at various times during desensitization and compare these changes with the clinical course and skin test results.

METHOD

Patients seen by the Allergy Service will be given the usual allergy evaluation to include clinical history, physical examination, appropriate skin tests, laboratory blood tests, and pulmonary function spirometry. A 5 cc aliquot of serum will be reserved and tested for specific IgE reagenic antibody titers by the RAST technique, performed by the Nuclear Medicine Service. Those patients who are placed on desensitization treatment will be reevaluated at appropriate intervals by the Allergy Service, at which time serum will again be drawn for repeat RAST titers and compared with skin test results and correlated with the clinical course.

PROGRESS

(79 10 - 80 09) Initial RAST titers to various pollens were obtained, and approximately 10 patients were placed on desensitization immunotherapy. There appears to be a correlation between RAST titer changes and endodermal skin test changes.

STATUS: (C)

TITLE: Immunotherapy of Murine Mammary Carcinoma

PRINCIPAL INVESTIGATOR: COL Clarence M. Virtue, MC

PROFESSIONAL ASSISTANTS: LTC Joel W. Black, MC
MAJ George S. Ward, VC

WORK UNIT NO: 77/77

TECHNICAL OBJECTIVE

Immunotherapy has as yet made only a minimal contribution to the treatment of malignant disease, due in large measure to the lack of pure tumor associated antigen. If tumor associated antigen were obtained in pure form and administered with Levamisole so as to enhance the anti-tumor immune response, after surgery and chemotherapy had reduced tumor load, results might be markedly improved. The purpose of this protocol is to explore that possibility, using mammary tumor-bearing mice.

METHOD

Murine mammary tumors from tumor-bearing mice will be excised, the tumor tissue homogenized in saline and freeze-thawed, and the supernatant concentrated by dialysis against dry silica gel and passed through G-200 sephadex column for separation. The separate fractions so obtained will then be concentrated and small aliquots of each fraction will be tested for tumor antigen by skin testing on the mice whose tumors have been excised. Fractions identified as having tumor associated antigens will then be processed by quantitative electrophoresis to separate the individual proteins. These individual fractions will be concentrated and the fraction containing tumor antigen will be identified by skin testing on tumor-excised mice. After identification of specific tumor antigen fractions, more will be separated from additional tumor and used to treat various groups of mice as outlined in the protocol. All groups of mice will be compared for length of survival.

PROGRESS

(79 10 - 80 09) C₃H mice have been divided into control and treatment groups with various treatment groups receiving Cytoxan and tumor vaccine prepared by Sephadex G-200 column separation. Mice have been given mammary tumor load and are under observation.

STATUS: (0)

TITLE: The Effect of Body Position on Arterial Oxygen Tensions in the Immediate Postoperative Period Following General Anesthesia

PRINCIPAL INVESTIGATOR: CPT Salvatore A. Ciresi, ANC

PROFESSIONAL ASSISTANTS: LTC Jorge I. Uribe, MC
Edward G. Pavlin, M.D.
Molly Tyler, R.N.

WORK UNIT NO: 80/42

TECHNICAL OBJECTIVE

To determine if select postoperative positions have a significant effect on arterial oxygen tensions.

METHOD

Twenty patients, age 20-60, without cardio-pulmonary disease will be studied in the immediate postoperative period following general anesthesia. After the patient is transferred to the recovery room and has been in the supine position for 10 minutes, arterial oxygen tensions will be monitored by percutaneous insertion of a 20-22 gauge teflon cannula in the radial artery. The patient's position will be changed by 10° until the patient has reach a 30° head-up position and measurements of PaO_2 will be done in each position. Then the patient will be lowered to the supine position with measurements taken again. Vital signs will be strictly monitored after each position change. Multi-variance analysis will be used to determine if a significant change in arterial oxygen tension can be attributed to one of the four positions.

PROGRESS

(80 05 - 80 09) A significant difference in ABG values (PaO_2) was found between upper and lower abdominal cases. The lower abdominal group ($n=5$) did not show any change with change in position. This group's PaO_2 values were surprisingly high immediately following general anesthesia. The upper abdominal group ($n=5$) did show an upward trend with the change in position, but the P value was greater than .05. The study did reinforce the fact that this particular surgical group does experience a mild/moderate degree of hypoxemia due to a reduction in FRC and the impingement of closing volume.

The Effect of Body Position on Arterial Oxygen Tensions in
the Immediate Postoperative Period Following General
Anesthesia - Ciresi

The routine use of O₂ for lower abdominal cases is being cri-
tically evaluated with a potential savings of \$10,000/year.
Ideally, another 20 patients should be studied. With more
staff support promised in the next fiscal year, tentative
plans are to reopen the protocol to study more subjects.

STATUS: (C)

TITLE: MATERNAL STRESS EFFECTS ON FETAL ACTIVITY

PRINCIPAL INVESTIGATOR: LTC Aida L. Rivera, ANC

PROFESSIONAL ASSISTANTS: COL Joseph Sakakini, MC
MAJ Raymond Parker, MSC

WORK UNIT NO: 79/84

TECHNICAL OBJECTIVE

To determine the effects of maternal anxiety and emotional stress on fetal activity during the last month of gestation.

METHOD

Subjects: 200 normatensive, married, primagravida women in the last month of gestation; age 19-30 years; weight gain <25 pounds. The subjects will be given the Taylor Manifest Anxiety Scale. The 30 patients with the highest scores and the 30 patients with the lowest scores will be tested by a 20 minute fetal monitoring tracing in order to determine the existence of any significant differences in fetal activity. Subjects will be followed to delivery and all data obtained from mothers who deliver abnormal fetuses will be deleted from the study. Factors other than stress (smoking, alcohol) will be identified and will be considered when tabulating results. This will be a double blind study and test scores will be ranked in a frequency distribution in order to pick the 30 highest and the 30 lowest scores. If ties scores are present, the needed scores will be drawn at random. The Split Plot Factorial Analysis of Variances - 2.3 will be used for computation of data.

PROGRESS

(79 10 - 80 09) All data has been collected and is being analyzed.

STATUS: (0)

TITLE: Hormonal Assay As a Predictor of Spontaneous Abortion
PRINCIPAL INVESTIGATOR: CPT Michael S. Phillips, MC
PROFESSIONAL ASSISTANT: LTC Stephen R. Plymate, MC
WORK UNIT NO: 79/76

TECHNICAL OBJECTIVE

To determine if, by measurement of one or a combination of hormones early in pregnancy, spontaneous abortion in the first or second trimester can be predicted.

METHOD

Two groups of patients (50 patients each) will be studied in a similar manner. Blood will be drawn for determination of prolactin, progesterone, estradiol, HCG, and sex steroid binding globulin at the initial visit and at two week intervals through the fourteenth week of pregnancy (12th week of gestation). Control patients will be solicited through inclusion of request with pregnancy kits and will be limited to those who are no more than eight weeks from the last menses at their evaluation (making a minimum of four blood samples for each patient).

The second group of patients will be those presenting at no more than eight weeks gestation as a threatened abortion. These patients will have blood samples drawn at 8, 10, 12, and 14 weeks of pregnancy.

Results will be analyzed both individually as predictors and in combination, hopefully to discover one assay or combination of assays that is 100% accurate in prediction of spontaneous miscarriage.

PROGRESS

(79 10 - 80 09) Blood samples were collected on 72 normal and 25 miscarriage patients. No significant data was obtained because of the low number of miscarriage patients available.

STATUS: (C)

TITLE: A Prospective Randomized Study of Vaginal and Abdominal Delivery of the Low Birth Weight Frank Breech Fetus: Cooperative Study

PRINCIPAL INVESTIGATOR: COL Joseph Sakakini, Jr., MC

PROFESSIONAL ASSTS: COL William Benson, MC
LTC Roger Spencer, MC
MAJ Alexander R. Smythe, MC

WORK UNIT NO: 80/14

TECHNICAL OBJECTIVE

To determine whether the uncomplicated low birth weight frank breech fetus presenting in labor should be delivered by cesarean section or if vaginal delivery is a safe method with minimal maternal and neonatal risks.

METHOD

Randomized selection of breech fetuses will be performed for vaginal and cesarean section deliveries. That group that is selected for cesarean section will be treated in the routine manner. The group that is randomized for vaginal delivery will be monitored, and, if they should show indications of fetal distress, heavy vaginal bleeding, prolapsed cord, or other indication for cesarean section, the cesarean section will be performed. A vaginal delivery will be performed if none of the listed indications for cesarean section are present. Following delivery, evaluations will be made for both the mothers and the infants.

PROGRESS

(80 04 - 80 09) After initial canvassing for patients, this protocol was terminated because of the small number of patients available that would fit the protocol criteria.

STATUS: (T)

TITLE: Fetal Heart Rate Response and Maternal Uterine Contraction Response to Amniocentesis in Pregnancy

PRINCIPAL INVESTIGATOR: Alexander R. Smythe, MAJ, MC

PROFESSIONAL ASSISTANT: Edward Blackmon, CPT, MC

WORK UNIT NO: 80/08

TECHNICAL OBJECTIVE

To quantitate the fetal heart rate response and uterine contraction response to amniocentesis at various gestational ages during pregnancy.

METHOD

Pregnant patients who undergo diagnostic amniocentesis for L/S ratio for reasons such as repeat cesarean section, medical or elective induction of labor for reasons such as diabetes hypertension, or Rh disease, or for premature labor and a premature fetus will be included in this study.

The patient will be placed on an external fetal monitor for fetal activity determination for 30 minutes prior to amniocentesis. A realtime ultrasound will be performed to assess the biparietal diameter and placental localization and amount of amniotic fluid present. An amniocentesis will be performed in the usual fashion and fetal heart rate response and uterine contraction pattern response will be assessed for 30 minutes after amniocentesis.

The measured parameters will be analyzed for indications of fetal stress or fetal well-being at the time of the performance of the amniocentesis. Comparison will be made with fetal parameters and uterine contractions for the baseline during the amniocentesis.

PROGRESS

(80 02 - 80 09) Approximately 35 patients have been entered in the study. Fetal monitoring has been done before and after amniocentesis and results are being tabulated. More patients are to be added to the study.

STATUS: (0)

TITLE: Impact of Fetal Monitoring on the Premature Infant

PRINCIPAL INVESTIGATOR: MAJ Alexander Smythe, MC

PROFESSIONAL ASSTS: COL Joseph Sakakini, MC
D. A. Luthy, M.D.
E. B. Larson, M.D.
K. K. Shy, M.D.
G. VanBelle, M.D.

WORK UNIT NO: 80/48

TECHNICAL OBJECTIVE

To analyze the effects of electronic fetal monitoring versus traditional auscultation in infants of very low birth weight with respect to the following endpoints: (1) perinatal mortality; (2) perinatal morbidity including Apgar scores, acid-base status at birth, and frequency of intracranial hemorrhage; (3) maternal morbidity including rates of cesarean section; (4) infant neurological and psychomotor development to one year of age; (5) provider satisfaction; (6) consumer satisfaction; (7) medical decision making; and (8) cost effectiveness analysis.

METHOD

Follow-up will be performed on infants who have had fetal monitoring. Those fetuses which have had electronic fetal monitoring and fetal scalp blood sampling done will be followed and compare to randomized traditional auscultation fetal heart rate. Comparisons of fetal outcome and wellbeing will be made. A comparison will be made of infants <1100 gm and >1100 gm. Infants will be followed and evaluated for evidence of retardation, cerebral palsy, and hearing loss at 6 months, 1 year, 1½ years, and 2 years.

PROGRESS

(80 06 - 80 09) No patients have been entered on the study. This is a group protocol. Patient entry will begin when organization among the groups involved has been standardized and funding difficulties have been resolved.

STATUS: (0)

TITLE: The Effect of In Vivo Vitamin B6 Supplementation on
In Vitro Lymphocyte Transformation

PRINCIPAL INVESTIGATOR: CPT Richard Keniston, MC

PROFESSIONAL ASSISTANTS: CPT Michael Smith, MSC
Louis Matej, M.T., DAC

WORK UNIT NO: 79/21

TECHNICAL OBJECTIVE

To demonstrate that optimum human lymphocyte transformation in vitro requires in vivo vitamin B6 (as pyridoxal phosphate, PLP). PLP is required for the biosynthesis of the polyamines, which are required for optimal DNA synthesis by nitrogen-stimulated T-lymphocytes. Most human beings are far from being saturated with PLP, and, therefore, their immune function might benefit from vitamin B6 supplementation.

METHOD

Normal volunteers: Ten male and ten female volunteers will follow the schedule below. All lymphocyte transformations (LT) will be done by the ^3H -thymidin uptake method without mitogen, using phytohemagglutinin and concanavalin A. Vitamin B6 assays will be completed on serum by an enzymatic method. Total blood drawn for both procedures will be 20 ml/drawing.

Schedule:

- 0 wks - L.T., B6 assay, begin multivitamins, p.o.
2 mg B6, q.d.
- 4 wks - L.T., B6 assay, begin B6 vitamins p.o.,
50 mg q.d.
- 6 wks - L.T., B6 assay
- 12 wks - L.T., B6 assay, end B6 supplementation
- 14 wks - L.T., B6 assay
- 20 wks - L.T., B6 assay, end multivitamin supplementation
- 24 wks - L.T., B6 assay

The magnitude of mitogen stimulation will be compared in steps 1-7. These will also be correlated with serum B6 levels.

Chronically ill volunteers: Chronically ill patients with apparent immune deficiency will be identified. B6 levels will be determined and the immune deficient patients will be given B6 supplementation. A condensed form of the schedule above will be followed. Any improvement in the patient's in vitro and in vivo immune response will be noted. In vitro response will be measured by lymphocyte transformation and in vivo response by clinical signs.

The Effect of In Vivo Vitamin B6 Supplementation on In Vitro Lymphocyte Transformation - Keniston

PROGRESS

(79 10 - 80 09) Thus far, urine reagents obtained for this project have demonstrated that the aminoglycoside antibiotics Kanamycin and Gentamicin and the antimicrobial Primaquine form covalent complexes with pyridoxal phosphate and could thus deplete vitamin B6.

Work continues on this project. One paper has been published, another has been submitted for publication, and other papers are being written.

STATUS: (0)

PUBLICATION: Keniston, R.C.: Polyamine-Pyridoxal 5'-Phosphate Interaction: Effects of pH and Phosphate Concentration on Schiff's Base Formation. *Physiol Chem Phys* 11:465-70, 1979.

PRESENTATION: Role of Vitamin B6 and Putrescine in Human Lymphocyte Activation: Beneficial Effect of Dietary Vitamin B6 Supplements. Joint Meeting, British Columbia Society of Clinical Chemists and American Association for Clinical Chemists (NW Section), 20-22 Sep 79, Harrison Hot Springs, BC.

TITLE: The Prevalence of *Chlamydia trachomatis* in Neonatal Pneumonia and the Antimicrobial Therapeutic Response of this Disease.

PRINCIPAL INVESTIGATOR: CPT Larry B. Mellick, MC

PROFESSIONAL ASSISTANT: LTC John K. Podgore, MC

WORK UNIT NO: 79/79

TECHNICAL OBJECTIVES

To further delineate the prevalence of *C. trachomatis* as an etiologic agent in neonatal pneumonitis and to compare the clinical efficacy of erythromycin and ampicillin in treating infants with chlamydial pneumonia.

METHOD

Approximately 30 infants with pneumonia and 30 control infants less than one year of age will be enrolled in the study. Controls will be hospitalized infants without pneumonia and will be matched according to race and age. With the exception of tear antibody, both groups of infants will have pertinent clinical data recorded and cultures for *C. trachomatis* will be obtained from the conjunctivae and nasopharynx. Tears, nasopharyngeal secretions and serum will be obtained for chlamydial antibody (tears will not be obtained from control infants). Serology will be done using the micro-immunofluorescence technique, utilizing specific anti IgG, IgM, and IgA conjugates. Serum will also be tested for total IgG and IgM in addition to routine diagnostic procedures. Cultures and serology will be done on admission, at discharge, and at one month post illness. Cultures will also be obtained on admission for viruses, *M. pneumoniae*, and pertussis. Serum will also be tested for the presence of the capsular antigen of *H. influenzae*, utilizing latex agglutination. Infants who meet the clinical criteria for *C. trachomatis* will be randomized to receive either erythromycin estolate suspension (35 mg/kg/day in 4 doses for 14 days) or ampicillin (50 mg/kg/day in 4 divided doses for 14 days). Capillary blood gases for PO₂ on days 1, 2, and 14 or discharge, chest x-ray on admission and 1 and 3 months post illness, and serum for SGOT and alkaline phosphatase on admission and day 7 or discharge will be done. X-rays will be coded and read blind by a radiologist and infants will be monitored for adverse effects of therapy.

The Prevalence of *Chlamydia trachomatis* in Neonatal Pneumonia and the Antimicrobial Therapeutic Response of This Disease - Mellick

PROGRESS

(79 10 - 80 09) Due to the departure of the principal investigator and difficulties obtaining subjects, this protocol has been terminated.

STATUS: (T)

TITLE: The Role of Bacterial and Chlamydial Agents in Acute Epididymitis and the Effect of Antibiotic Therapy

PRINCIPAL INVESTIGATOR: LTC John K. Podgore, MC

PROFESSIONAL ASSISTANTS: CPT Robert U. Finnerty, MC
COL Alfred S. Buck, MC

WORK UNIT NO: 78/20

TECHNICAL OBJECTIVE

To determine what role certain infectious agents (*Mycoplasma*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and aerobic coliform bacteria) play in the etiology and pathogenesis of acute epididymitis; and to compare two commonly used forms of therapy for treatment of epididymitis.

METHOD

Study population: All males seen with the diagnosis of acute epididymitis who are hospitalized at Madigan Army Medical Center and who have had no antibiotic therapy in the month preceding the current episode of epididymitis.

Controls: A group of age and race-matched controls will be selected from Ft Lewis military personnel undergoing routine physical examinations.

Two urethral swabs will be obtained using calcium alginate swabs; the first for culture of *N. gonorrhoeae* and Gram stain; the second for culture of *C. trachomatis* and *U. urealyticum*.

Urine specimens: The first 10 cc of voided urine and a mid-stream urine will be obtained. The sediment of the first voided urine and midstream urine will be examined for number of WBC per high-powered field and bacteria. Both urine specimens will be cultured quantitatively for coliforms.

Blood specimens: 10 cc will be obtained by venipuncture for serology for *C. trachomatis*.

Similar urine and blood specimens will be obtained from the controls.

When surgery is clinically indicated to rule out torsion of the testicle, direct cultures of epididymal fluid will be

The Role of Bacterial and Chlamydial Agents - Podgore

obtained at scrotal exploratory surgery. Radionucleotide scrotal scans will be done on all patients within 48 hours to rule out testicular torsion.

Treatment: All patients will be placed at bed rest with scrotal elevation until afebrile and pain has subsided.

If no coliforms are seen on the initial unspun urine and the midstream urine culture shows less than 10^3 coliforms per ml, the patient will be randomly treated with 100 mg doxycycline b.i.d. for 10 days or with 500 mg ampicillin q.i.d. for 10 days. If the patient's medical records or history indicate possible allergy to either of these agents, the alternate safe agent will be administered.

If coliforms are seen on the initial unspun urine or grown from any specimen with colony counts greater than 10^3 /ml, patients will be treated individually according to results of urine cultures and antibiotic sensitivity patterns. Patients will be instructed not to have intercourse for at least 14 days after initiation of treatment.

Follow-up: All patients will be reexamined at 3, 7, 14 days, and 6 weeks after initiation of therapy. The presence of scrotal erythema, edema, and tenderness will be noted and recorded by standard protocol. Repeat cultures will be performed at 7 and 14 days and 6 weeks for *C. trachomatis*, *C. trachomatis*, and any other pathogen initially recovered. Ten cc of convalescent blood will be obtained for serologic testing at 14 days and 6 weeks.

PROGRESS

(79 10 - 80 09) Investigators are still in the process of collecting data. When at least 50 patients have been entered in the protocol, the data will be analyzed.

STATUS: (0)

TITLE: The Effect of Antibiotic Therapy in the Last Trimester of Pregnancy Upon the Incidence of Neonatal Conjunctivitis and Pneumonia Due to *Chlamydia trachomatis*.

PRINCIPAL INVESTIGATOR: LTC John K. Podgore, MC

PROFESSIONAL ASSISTANTS: LTC Errol Alden, MC
MAJ Richard Belts, MC
Catherine Yokan, M.D., DAC

WORK UNIT NO: 78/38

TECHNICAL OBJECTIVE

To determine the effect of treatment with erythromycin, 500 q.i.d. for 14 days, administered orally to pregnant women during the last trimester of pregnancy with cervical *Chlamydia trachomatis* colonization. The incidence of subsequent neonatal colonization and conjunctival and pulmonary infection will be noted in treatment and control infants over a one-year interval after delivery.

Addendum: The effect of erythromycin therapy on the vaginal and neonatal carriage of this organism will be simultaneously studied.

METHOD

Cervical specimens will be obtained on sterile cotton swabs during the routine 32-week pelvic examination.

Serum specimens will be obtained from a portion of blood routinely drawn for rubella antibody screening. The microimmunofluorescent serology for chlamydia will be done according to standard methods.

Conjunctival and nasopharyngeal specimens will be obtained during the nursery discharge examination and at the 4 week, 2 month, and 6 month examinations.

Serum specimens will be obtained from the study children at 6 and 12 months for the microimmunofluorescent serology titer for chlamydia.

Conjunctival specimens will be obtained from all study infants that present with acute conjunctivitis for Giemsa stains, bacterial and chlamydial cultures.

The Effect of Antibiotic Therapy in the Last Trimester of
Pregnancy - Podgore

Nasopharyngeal specimens will be obtained for Gram stain, bacterial, and chlamydial culture in all study infants presenting with pneumonia during the first year of life.

All patients with positive chlamydial cultures will be assigned randomly into the treatment and non-treatment groups. The treatment group will receive 500 mg erythromycin q.i.d. for 14 days.

Culture of the vaginal vault and rectum for Group B streptococci prior to and following therapy with erythromycin will be done.

PROGRESS

(79 10 - 80 09) Erythromycin administered to women in the third trimester of pregnancy and their spouses was effective in eradicating *Chlamydia trachomatis* and preventing neonatal infection.

STATUS: (0)

PRESENTATION: Podgore, J.K., Belts, R., Alden, E., and Alexander, L.R.: Effectiveness of Maternal Third Trimester Erythromycin in Prevention of Infant *Chlamydia trachomatis* Infection. 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, sponsored by American Society for Microbiology, 22-24 September 1980, Abstract #524.

TITLE: A Survey of *Chlamydia trachomatis* Cervical Colonization in Late Pregnancy and Conjunctival and Naso-Pharyngeal Carriage in the First Six Months of Life

PRINCIPAL INVESTIGATOR: LTC John K. Podgore, MC

PROFESSIONAL ASSISTANTS: LTC Errol Alden, MC
MAJ Richard Belts, MC
CPT Larry Mellick, MC
Catherine Yordan, M.D., DAC

WORK UNIT NO: 78/41

TECHNICAL OBJECTIVE

To determine the baseline carriage rate of *Chlamydia trachomatis* in the endocervix during late pregnancy and its relationship to various factors including age, parity, socio-economic status, race, and the development of subsequent post-partum fever, neonatal conjunctivitis, and pneumonia.

METHOD

The study population will consist of pregnant military dependents seen at MAMC during the 35 week gestation examination and all infants of these women. Cervical specimens will be obtained on sterile cotton swabs during the 35 week pelvic examination, immediately placed into carrying medium and stored at -70°C and transported to the isolation laboratory at the University of Washington weekly. Serum specimens will be obtained from a portion of blood routinely drawn at this time. Microimmunofluorescent serology for chlamydia will be done according to standard methods. Conjunctival specimens and naso-pharyngeal specimens will be obtained at the nursery discharge examination and at 4 weeks, 2 months, and 6 months. Conjunctival specimens for Giemsa stain and bacterial and chlamydial cultures will be obtained from all study infants that present with acute conjunctivitis as will naso-pharyngeal specimens for Gram stain. Bacterial and chlamydial cultures will be obtained from all study infants that present with pneumonia during the first year of life. Serum will be obtained from all study infants at six months to measure serum antibody to chlamydia by microimmunofluorescent methods.

A Survey of *Chlamydia trachomatis* Cervical Colonization in
Late Pregnancy and Conjunctival and Naso-Pharyngeal Carriage in
the First Six Months of Life - Podgore

PROGRESS

(79 10 - 80 09) A number of patients were selected for this study. Results of 365 cultured patients revealed an 11% colonization rate. Due to the proximity of the objectives of the two studies, this study has been incorporated into the study entitled "The Effect of Antibiotic Therapy in the Last Trimester of Pregnancy Upon the Incidence of Neonatal Conjunctivitis and Pneumonia Due to *Chlamydia trachomatis*", which is also being conducted by Dr. Podgore and his associates.

(C)

TITLE: The Role of *Campylobacter* in Pediatric Enteritis

PRINCIPAL INVESTIGATOR: LTC John K. Podgore, MC

PROFESSIONAL ASSISTANTS: MAJ Martin Crumrine, MSC
CPT Larry Mellick, MC

WORK UNIT NO: 79/09

TECHNICAL OBJECTIVE

To determine the role of *Campylobacter* in acute diarrheal disease of childhood.

METHOD

To determine the role of *C. fetus* in acute diarrhea of childhood, rectal swabs taken from a group of children presenting with acute diarrhea will be placed in selective medium and atmospheric conditions for campylobacter organisms as well as routine bacterial studies for enteric organisms. A group of children presenting for problems other than diarrhea will be selected as matched controls to determine the carriage of *C. fetus* in the general pediatric population.

Patients presenting with acute diarrhea and control patients will have rectal swabs obtained and placed in Stuart's transport medium and then plated on selective campylobacter medium in less than 6 hours for overnight culture. The selective medium consists of blood agar with the addition of Vancomycin (10 mg/L), polymyxin B (2.5 IU/ml), and trimethoprim (5 mg/L). These plates will then be incubated at 43°C in an atmosphere of 5% oxygen, 10% carbon dioxide and 85% hydrogen overnight. The swabs will also be processed in the usual manner for enteric organisms.

PROGRESS

(79 10 - 80 09) Eighty-nine (89) patients presenting with acute diarrhea were cultured for *Campylobacter fetus ss jejuni* and other enteric pathogens. *C. fetus ss jejuni* was isolated from six of these cases. No other enteric pathogens were isolated from these patients. *C. fetus ss jejuni* may be a more significant pathogen than *Salmonella* or *Shigella* in this population.

STATUS: (C)

TITLE: Transmission of *Chlamydia trachomatis* Between Family Members

PRINCIPAL INVESTIGATOR: LTC John K. Podgore, MC

PROFESSIONAL ASSISTANTS: Linda L. McDonald, R.N.
E. R. Alexander, M.D.
LTC Richard P. Belts, MC

WORK UNIT NO: 79/94

TECHNICAL OBJECTIVE

To determine the incidence of transmission of *C. trachomatis* among family members, especially among siblings of neonates born to cervically colonized and non-colonized mothers.

METHOD

Cervical cultures for *C. trachomatis* and serum samples for antibody will be obtained from mothers at the 32 week OB visit. Fifty women found to have positive cervical cultures, having at least one child present in the home, will be studied. The cases will be matched with a culture negative control mother matching in maternal age within five years and the number of children in the respective homes. A portion of the colonized mothers will be treated prenatally with 14 days of oral erythromycin so that such treatment effects on transmission in this subset of cases will be noted. Husbands will have urethral cultures taken as well as serum drawn for chlamydial antibody on entry into the project. Siblings will have baseline serum and tear antibody studies as well as conjunctival and nasopharyngeal cultures at entry and at two and six months post partum. Neonates will have conjunctival and nasopharyngeal cultures done during the discharge exam and at the two week, two and six month pediatric exams. Serum and tear antibody studies will be done at the six month exam. All participants will be followed for conjunctivitis and/or respiratory disease as well as cultured at two and six month intervals to determine nasopharyngeal and conjunctival colonization. Baseline and terminal antibody studies will be done to illustrate conversion rates. Routine bi-weekly phone surveys and home visits will be done as required to assess illness in subjects not requiring clinic visits.

Transmission of *Chlamydia trachomatis* between Family
Members - Podgore

PROGRESS

(79 10 - 80 09) This project was terminated due to the lack of patients. There was not enough transference among family members in the subjects studied to obtain a significant study population.

STATUS: (T)

TITLE: Cryopreservation of Human Platelets for Transfusion

PRINCIPAL INVESTIGATOR: CPT Dennis E. Urban, MSC

PROFESSIONAL ASSISTANTS: MAJ Robert Ridgway, VC
MAJ Robert Usry, MSC
MAJ Joseph Yetter, MC
CPT Kris Shekitka, MC

WORK UNIT NO: 77/06

TECHNICAL OBJECTIVE

To preserve platelets for transfusion by freezing.

METHOD

Phase I. Freeze and recover platelets.

- a. Screen 10 healthy routine blood donors of O positive blood including:
 - (1) normal donor criteria
 - (2) platelet count
 - (3) salicylate level
- b. Draw one unit of blood from each donor.
- c. Red cells and other components to be used routinely by the Blood Bank.
- d. Preparation of platelets for freezing in accordance with the Dayian and Rowe procedure.
- e. Aliquot each prepared platelet pack to be used as control and for testing.
- f. Thaw platelets after 36 hours by submersion in a 40°C water bath with mild agitation for 20 seconds.
- g. Sample control and test for bacteriologic control. Culture by the automated bacterial detection method on blood agar and peptone broth.
- h. Test both test and control samples for platelet count and osmolality of platelet concentration.

Phase II.

- a. Screen 20 healthy routine blood donors of O positive blood including:
 - (1) normal donor criteria
 - (2) platelet count
 - (3) partial thromboplastin time
 - (4) salicylate level

Cryopreservation of Human Platelets for Transfusion - Urban

- b. Draw one unit of blood. Red cells and other components minus PRP to be used routinely by blood bank.
- c. Preparation of platelets for freezing (see paragraphs e-h, Phase I).
 - d. Test platelets, frozen and nonfrozen, for viability of recovered platelets in accordance with criteria established by Dayain and Rowe (Cryobiology 13:1-8, 1976).
 - (1) uptake of ^{14}C serotonin
 - (2) (a) ADP induced aggregation
 - (b) Epinephrine induced aggregation
 - (c) collagen induced aggregation
 - (3) clot reaction
 - (4) response to hypotonic shock
 - (5) platelet recovery and size distribution
 - (6) osmolality of platelet concentration

PROGRESS

(79 10 - 80 09) Data was generated and an article published. Project was terminated due to lack of personnel and a shift in emphasis from glycerol-frozen platelets to DMSO-frozen platelets.

STATUS: (C)

PUBLICATION: Ridgway, R.C. and Usry, R.T.: Cryopreservation of Platelets Simplified: A Modified Glycerol-Glucose Method. Transfusion 20:427-32, 1980.

PRESENTATION: Valeri, C.R. and Roth, R.R.: Cyropreservation of Platelets. 4th Annual Meeting of the Society of Armed Forces Medical Laboratory Scientists, Seattle, WA, 11 Oct 78.

TITLE: Rejuvenation of Outdated Human Erythrocytes and Evaluation of Frozen Blood Techniques

PRINCIPAL INVESTIGATOR: CPT Dennis Urban, MSC

PROFESSIONAL ASSISTANTS: CDR C. Robert Valeri, MC, USNR
LTC Marshall E. Hinckley, MC
MAJ William J. Hunter, MC
CPT Kris Shekitka, MC
Dolores LaBarge, MT, DAC

WORK UNIT NO: 77/45

TECHNICAL OBJECTIVE

To determine the safety and efficacy of human red cells stored at 4°C for 22-28 days that are biochemically modified (rejuvenated) prior to freeze-preservation; and to evaluate two techniques to freeze and deglycerolize human erythrocytes for utilization at Madigan Army Medical Center.

METHOD

Phase I: Rejuvenate and refreeze 30 units outdated O-positive or O-negative red cells and ship to the Naval Blood Research Laboratory, Boston, MA, for complete freeze-thaw-wash recoveries on the red cells, bacterial cultures, and measurement of the red cell 2, 3-DPG, ATP, and potassium ion levels in addition to in vitro P_{50} levels. Red cell survival measurements will be performed on selected units.

Phase II: Rejuvenate and refreeze 30 units of expired blood, the same as Phase I with the exception of the removal of the supernatant solution containing glycerol, the solution used for biochemical modification, and plasma that is present in the concentrated red cells prior to freezing. These units will be shipped and evaluated as in Phase I.

Phase III: Same procedures as in Phase II with the exception that freezing will be accomplished in the original blood bag and shipped as in Phase I and II.

PROGRESS

(79 10 - 80 09) Restoration of ATP and 2,3-DPG levels on 25 units of outdated blood stored in CPD preservative was accomplished utilizing Valeri's PICP-A and PICP-B solutions. Additional units were rejuvenated and frozen and 2,3-DPG levels

Rejuvenation of Outdated Human Erythrocytes and Evaluation
of Frozen Blood Techniques - Urban

were performed. This method appears to be a feasible
method for rejuvenation of out-dated blood stored in CPD
preservative.

STATUS: (C)

TITLE: A Teaching Model for Pediatric Intubation Utilizing Ketamine-Sedated Kittens

PRINCIPAL INVESTIGATOR: C. Errol R. Alden, MC

PROFESSIONAL ASSISTANTS: LTC Paul E. Jennings, VC
MAJ Ronald W. Brenz, MC

WORK UNIT NO: 74/19

TECHNICAL OBJECTIVE

To teach infant resuscitation procedures to nurses, nurse clinicians, OB-GYN residents, and other nonpediatric physicians who may be called upon to treat pediatric emergencies. Many physicians and paramedics have never had the training opportunity to attempt intubation of an awake living creature. The kitten, immobilized with ketamine hydrochloride, gives the student the opportunity to visualize vocal cords, precipitate laryngospasm, and learn the difficulties associated with emergency intubation.

METHOD

Weaned kittens, weighing 0.5 to 1.0 kg will be used in these teaching sessions. Ketamine hydrochloride (22 mg/kg) plus atropine sulfate (0.04 mg/kg) will be administered intramuscularly to each kitten. Intubation will be performed with the kittens on their backs, using a pediatric laryngoscope, and sizes 8-14 French endotracheal tubes. Kittens may be used for several consecutive weekly sessions until they grow too large to be utilized. The procedure is not harmful to the kittens.

PROGRESS

(79 10 - 80 09) A teaching model for pediatric intubation, utilizing ketamine-sedated kittens, has been provided for physicians and ancillary medical personnel at Madigan. A dosage of 22 mg/kg of ketamine, administered IM to weaned kittens, produces some sedation but maintains laryngeal reflexes comparable to the awake human neonate. Practice sessions with this living model continue to fulfill a needed requirement for medical personnel who may be called upon in pediatric emergencies.

STATUS: (0)

A Teaching Model for Pediatric Intubation Utilizing Ketamine-Sedated Kittens - Alden

PUBLICATION: Jennings, P.B., Alden, E.R., and Brenz, R.W.: A Teaching Model for Pediatric Intubation Utilizing Ketamine-Sedated Kittens. Pediatrics 53:283-84, 1974.

EXHIBIT: Alden, E.R. and Jennings, P.B.: Animal Models for Neonatal Resuscitation.

- a. Annual Meeting of the American Academy of Pediatrics, Chicago, IL, Oct 1976. Gold Award for Outstanding Exhibit for Teaching Value.
- b. Annual Meeting of the American Medical Association, San Francisco, CA, Jun 1977. Certificate of Merit
- c. American Veterinary Association Atalnata, GA, Jul 1977.
- d. Annual Meeting of the Association of Military Surgeons, Washington, DC, Nov 1977.

TITLE: Ambulatory Adolescent Health Care Needs: Implications for Pediatric Training Programs

PRINCIPAL INVESTIGATOR: COL. Errol R. Alden, MC

PROFESSIONAL ASSISTANTS: Peter E. Johnsen, M.D.

WORK UNIT NO.: 78/39

TECHNICAL OBJECTIVE

To determine from collated data of all Adolescent Clinic visits for one year (1) the common health care needs of this population of adolescents; (2) where the focus of teaching effort should be in training residents; and (3) in which areas useful research could be entertained. This study will also serve as a quality control function for the Adolescent Clinic.

METHOD

For one calendar year, assign each new patient a file card, including name, SSN, year of birth, sex, race, sponsor's rank, and status. For each patient visit, the physician will write the diagnoses of the problems encountered on that visit on the file card to be coded by the clinic staff. At the end of the year, the following data will be tabulated: (1) number of patients/patient visits; (2) number of patients/patient visits for each diagnostic category; and (3) demographic data: sex, year of birth, race, sponsor's rank and status. The collated data will then be evaluated for those areas in which resident education would be beneficial and a curriculum derived.

PROGRESS

(79-10 - 80-09) The study supports the impression of adolescent specialists that pediatricians with adolescent patients would benefit from training in the areas of normal adolescent growth and development (physical and psychological), interviewing skills, facility in managing psychosocial and psychosomatic problems, and skills in the management of the obstetric/gynecologic needs of this population. In addition, the need for specific training in the recognition and optimal management of common orthopedic problems should be emphasized. A manuscript has been written and is being revised for publication.

STATUS: (C)

TITLE: The Role of Varicella in the Induction of Pediatric Renal Disease

PRINCIPAL INVESTIGATOR: CPT Marvin Bergeson, MC

PROFESSIONAL ASSISTANTS: LTC John Podgore, MC
MAJ Lawrence Agodoa, MC
CPT Bruce Cook, MC

WORK UNIT NO: 79/80

TECHNICAL OBJECTIVE

To determine the incidence and extent of renal involvement following varicella infection.

METHOD

Urine specimens will be obtained at initial diagnosis of varicella infection. Urinalysis will be repeated at 2 weeks and 3 months after the clinical onset of the varicella infection. The following laboratory studies will be obtained on patients with an active urine sediment at the initial, 2 week, and 3 month examinations: CBC; ESR; platelet count; SMA-20; streptozyme; ASO titer; ADB titer; C₃; C₄; CH-50; ANA; RA; VDRL; and HAA. Study patients with an active urine sediment will have a throat culture for beta-hemolytic streptococci by standard methods on the initial visit. Skin culture will be taken from the healing crusted varicella lesions of patients with an active urine specimen at the initial, 2 week, and 3 months examinations. Serum specimens will be collected for varicella titer at the initial, 2 week, and 3 months examinations on patients with an active urine specimen. The first ten patients with leukocytes in their urine will have fluorescent antibody staining for varicella zoster and cytology for viral inclusions. The first ten patients will have viral culture on their urine specimens.

PROGRESS

(79 11 - 80 09) This project was never initiated due to the unexpected reassignment of the principal investigator and one of the co-investigators.

STATUS: (T)

TITLE: Evaluation of New Technique for Bone Marrow Biopsy

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANTS: COL Jack Frost, DC
LTC Irwin Dabe, MC
LTC Arthur Krakow, DC
MAJ George Ward, VC
MAJ Rehka Dhru, MC
MAJ Alan Mease, MC

WORK UNIT NO: 80/68

TECHNICAL OBJECTIVE

To develop instrumentation and technique for rapid bone marrow biopsy in children using high speed dental drill and a comparison of standard technique with Jamishidi & Illinois needle vs dental drill technique in animal system for: a. accuracy of histology; b. technical feasibility; c. pain decrease; and d. speed of procedure.

METHOD

Animal model: biopsy - iliac crest one side with classic technique and opposite side with new dental drill; cross-check smears for distortion and accuracy of sampling. To achieve different patient size simulation, 3 groups of animals will be used with at least 3 animals in each group. Animals used will be sheep, large dogs, and small dogs. Animals will be anesthetized with a general anesthetic. The reviewer of the slides will have no prior knowledge of which procedure was used to obtain the samples. If samples prove to be of good quality, a follow-up protocol will be prepared for human application.

PROGRESS

(80 08 - 80 09) Instrumentation is still being explored. A new needle is being sought.

STATUS: (0)

TITLE: Self-Inflating vs Flow-Inflating Resuscitation
Bags: A Comparison and Development of A Teaching
Model

PRINCIPAL INVESTIGATOR: MAJ Philip V. Marinelli, MC

PROFESSIONAL ASSISTANTS: COL Errol R. Alden, MC
MAJ Amil Ortiz, MC
MAJ Lawrence Wickham, MC

WORK UNIT NO: 80/06

TECHNICAL OBJECTIVES

- (1) To evaluate respiratory parameters (i.e., tidal volume, PIP, PEEP) of three main types of manual resuscitation bags;
- (2) To determine respiratory frequency most commonly employed (stated vs actual);
- (3) To assess the "feel" of bagging, i.e., the clinical determination of lung compliance;
- (4) To underscore the need for continuous airway pressure monitoring;
- (5) To develop an experimental model for teaching and reinforcement of proper ventilatory techniques in newborn resuscitation to medical and paramedical personnel.

METHOD

Fifty physicians and 30 nurses at Madigan will be asked to test the bags. Another 300 physicians will be solicited for participation at the Uniformed Services Meeting. A Bourns Infant Lung Simulator and the Hewlett Packard Respiratory Integrator will be monitored while using the bags. Respiratory frequency, tidal volumes, PIP, and PEEP will be recorded and graphically displayed. The volunteers will be asked for their subjective evaluations of the parameters. A comparison of these subjective parameters will be made to the recorded findings.

PROGRESS

(80 01 - 80 09) Thirty-three members from four departments at Madigan have been analyzed. More members of the staff will be asked to participate.

STATUS: (0)

TITLE: A Pediatric Military Survey of Newborn Resuscitation

PRINCIPAL INVESTIGATOR: MAJ Philip V. Marinelli, MC

PROFESSIONAL ASSISTANTS: COL Errol R. Alden, MC
MAJ Amil Ortiz, MC
MAJ Lawrence Wickham, MC

WORK UNIT NO: 80/07

TECHNICAL OBJECTIVES

To document and critically evaluate how newborn resuscitative measures are presently performed at military facilities throughout the world with specific attention to bag preference and methods of monitoring airway pressure, and to determine if there is a difference in management between MEDDACS and MEDCENS.

METHOD

A questionnaire with 15 questions will be mailed to all military pediatricians and nurse practitioners. The replies will be statistically analyzed to determine the type of resuscitation bag most commonly used and how airway pressure is monitored. This information can be related to institution size, branch of service and time of training.

PROGRESS

(80 01 - 80 09) Three hundred and forty-four (344) of 483 questionnaires have been returned and are undergoing statistical analysis.

STATUS: (0)

TITLE: Peripheral Arterial Catheterization

PRINCIPAL INVESTIGATOR: MAJ Philip V. Marinelli, MC

PROFESSIONAL ASSISTANTS: COL Errol R. Alden, MC
MAJ Lawrence Wickham, MC

WORK UNIT NO: 80/61

TECHNICAL OBJECTIVE

As peripheral arterial catheterization is a relatively new manner of obtaining blood gases in a small neonate, a chart review will be undertaken to assess the relative merits of the multiple sites used by different investigators.

METHOD

A chart review will be done of patients at Tripler and Madigan Army Medical Centers. The chart of each infant treated in the intensive care unit will be reviewed, and, if, the infant had a peripheral arterial catheterization, this will be indicated. The site catheterized as well as complications will be detailed in the chart.

PROGRESS

(80 07 - 80 09) Charts have been reviewed and a manuscript is in preparation. Of 22 radial artery catheters, nine posterior tibial artery catheters, and two temporal artery catheters, two complications were noted with radial artery catheters and one with posterior tibial artery catheters. The only permanent sequela encountered was a small necrotic area developed on the great toe.

STATUS: (C)

TITLE: The Clinical Pharmacology of Methylphenidate

PRINCIPAL INVESTIGATOR: CPT Allen Neese, MC

PROFESSIONAL ASSISTANTS: LTC Daniel Anderson, MC
LTC Carl Plonsky, MC
CPT Michael Smith, MSC

WORK UNIT NO: 79/60

TECHNICAL OBJECTIVE

To determine the biological half-life of methylphenidate and ritalinic acid in children, the corresponding volume of distribution, therapeutic plasma concentrations, and plasma protein binding of these compounds.

METHOD

Approximately 50 children receiving methylphenidate therapy for minimal brain dysfunction will be given their usual dose of the drug, and blood samples will be taken at 0, $\frac{1}{2}$, 1, 2, 4, and 6 hours by an in-dwelling heparin lock. Urine will be collected for the 24 hours following dosing in 3 hour aliquots for the first 12 hours and in 6 hour aliquots for the last 12 hours. Both blood and urine will be assayed for methylphenidate and ritalinic acid to determine the corresponding pharmacokinetic parameters. Methylphenidate and ritalinic acid levels will be measured by either radioimmunoassay or gas chromatography. Correlation will be made between clinical response and plasma levels and/or half-life. A questionnaire entitled "Learning and Behavioral Intake" will be completed by a parent when the child enters the study. Clinical response to medication will be assessed at monthly intervals by interviews with both teacher and parent questioning the child's school performance, attention span, distractibility, emotional lability, impulsiveness, and fine motor coordination. A behavior checklist will be completed by the teacher at 8 week intervals.

PROGRESS

(80 02 - 80 09) Due to the lengthy approval procedure for this protocol, the departure of the principal investigator and the co-investigators was imminent when approval was received. Therefore, the protocol was terminated.

STATUS: (T)

TITLE: Tension Pneumothorax - A Teaching Model

PRINCIPAL INVESTIGATOR: MAJ Amil Ortiz, MC

PROFESSIONAL ASSISTANTS: LTC Errol Alden, MC
MAJ George S. Ward, VC

WORK UNIT NO: 76/29

TECHNICAL OBJECTIVE

To provide training in diagnostic and surgical skills in the treatment of tension pneumothorax and to provide ongoing teaching sessions.

METHOD

New Zealand white rabbits weighing 700-2500 grams are anesthetized initially with an intramuscular injection of ketamine hydrochloride and promazine hydrochloride. Five minutes after injection, the chest wall is shaved and prepared for surgery. EKG leads are placed on the rabbit and the heart rate and QRS voltage monitored on an oscilloscope. Surgical procedure as outlined in protocol. During the training session, the pathophysiology of TPT is discussed with each student. The entire training session can be accomplished in less than two hours for a group of 3 to 5 people.

PROGRESS

(79 10 - 80 09) A tension pneumothorax induced in a small rabbit is an excellent teaching model for the treatment of tension pneumothorax in the small human neonate. The rabbit model is inexpensive, readily available, and recreates the clinical condition of a tension pneumothorax in an educational environment. This continues to be a valuable teaching model with sessions held on a regular basis for pediatric personnel, ICU students, interns, and residents. Due to the departure of MAJ Ortiz, LTC P. Gary Pettett, MC, has assumed the role of principal investigator of this protocol.

PUBLICATION: Henderson, R., Alden, E., Jennings, P.B., and Hofmann, J.R.: Tension Pneumothorax - A Teaching Model. Pediatrics 58:861-62, 1976.

PRESENTATION: (Exhibit) Jennings, P.B., Alden, E.R., and Henderson, R.W.: Teaching Models for Neonatal Resuscitation. Annual Meeting of the Association of Military Surgeons of the United States, Nov 1977, Washington, DC.

STATUS: (0)

130

TITLE: The Neonatal Cardiac Index, A Valuable Prognosticator of Neonatal Well-Being

PRINCIPAL INVESTIGATOR: MAJ Amil Ortiz, MC

PROFESSIONAL ASSISTANTS: MAJ Bernard R. Hannam, MC
MAJ Lawrence K. Wickham, MC
SP4 Bret A. Hargrave

WORK UNIT NO: 79/68

TECHNICAL OBJECTIVE

The Neonatal Cardiac Index (NCI) during the first 24 hours of life, together with the APGAR scores can serve as a valuable tool in predicting the outcome of neonatal life. Patterns of heart rate during this period of time reflect the ability of the newborn myocardium to react to endogenous stimuli of catecholamines as well as exogenous stresses and developmental factors. The investigators propose to study this parameter in the premature infant of different gestational ages.

METHOD

A total of 100 premature newborns will be separated in groups of 25 according to gestational age (28-30 weeks, 30-32 weeks; etc.). All infants will have cardiorespiratory monitoring in the first 5 minutes of life, at 1, 12, and 24 hours of age. A Corometrics 512 neonatal monitor will be utilized as it is the only monitor with the capability of assessing beat to beat variations in heart rate. Upon delivery of the infant, a sample of 0.5 cc of heparinized blood will be taken from the placental side of the umbilical cord for the purpose of blood gas determination. The neonatal cardiac index and variability patterns will be determined in each monitoring period. A correlation of the NCI with the APGAR scores, blood pH, and gestational age will be made as well as the outcome of the infant.

PROGRESS

(79 10 - 80 09) This protocol is completed. The neonatal cardiac index is a very valuable prognosticator of not only neonatal well-being, but of mortality and morbidity. A manuscript is in preparation for submission for publication.

STATUS: (C)

TITLE: Standardization of a Screening Instrument for Developmental Soft Signs in Normal Children

PRINCIPAL INVESTIGATOR: LTC Carl A. Plonsky, MC

PROFESSIONAL ASSISTANT: CPT Heather Smith, MC

WORK UNIT NO: 79/16

TECHNICAL OBJECTIVE

To devise and standardize a screening examination for neurodevelopmental soft signs. Standardization will be done on a large number of normal children. The examination will then be given to a number of children with known minimal brain dysfunction and the results compared.

METHOD

A soft signs screening examination, method manual, and score sheet have been devised. The screening examination will be individually administered to 100 normal children, grades kindergarten through third grade. Thirty children will be tested by more than one examiner on the same day as a test for inter-examiner reliability, and 30 children will be re-tested one week later as a test of test-retest reliability. The age at which each of the developmental signs is found to be absent in 90% of this normal population will be calculated and tabulated. A sample of children with known MBD will be given the examination and the results compared to those of the normal population. After the pilot study is completed, the test instrument will be evaluated and refined and given to the entire on-post school population, kindergarten through third grade.

PROGRESS

(79 09 - 80 09) Comparison shows that the group of soft signs, when taken together as a total score, support the concept of measurement of neurodevelopment maturation in the school age child. The soft sign examination performed on children with minimal brain dysfunction is statistically significantly different from scores obtained in the control subjects. These findings are supportive of the conclusion that minimal brain dysfunction is a neuromaturational delay. An article for publication is in the process of being written.

Standardization of a Screening Instrument for Developmental
Soft Signs in Normal Children - Plonsky

STATUS: (0)

PRESENTATION: Plonsky, C and Smith, H.: The Soft Neurological
Signs in School-Age Children. Presented to
American Academy of Pediatrics, 15 Oct 79,
San Francisco, CA.

TITLE: Serum Cortisol and Incidence of Hyaline Membrane in Premature Sheep Pretreated with Steroids: Single vs Multiple Gestations

PRINCIPAL INVESTIGATOR: MAJ Lawrence Wickham, MC

PROFESSIONAL ASSISTANTS: MAJ Bernard Hannam, MC
MAJ Amil Ortiz, MC
MAJ George S. Ward, VC
CPT Michael Byrne, MC

WORK UNIT NO: 79/81

TECHNICAL OBJECTIVE

To attempt to show increased incidence HMD in multiple gestation pregnancies, even if pretreated with steroids; then to treat a second group of multiple gestation sheep with an increased dose of steroids and compare rates of HMD Group 1 to Group 2.

METHOD

Three groups of 4 sheep will be studied: Group A - single fetus; Group B - two or more feti; Group C - two are more feti. Groups A and B will be given a standard dose of steroid at less than 135 days gestation and Group C will be given twice the standard dose of steroids.

Amniocentesis will be performed at 24 and 48 hr post-steroid injection for L/S ratio determination.

At delivery - approximately 72 hrs after steroids - maternal and fetal cortisol levels will be drawn. A maternal cortisol will have been determined before any experimental manipulation.

Newborn gastric aspirate or tracheal aspirate L/S ratios will be obtained.

Lambs will be watched for respiratory distress syndrome. Lung tissue will be obtained for pathologic diagnosis of hyaline membrane disease from all neonatal mortalities or up to 50% of the survivors will be sacrificed to obtain this tissue.

Serum Cortisol and Incidence of Hyaline Membrane in Premature Sheep Pretreated with Steroids: Single vs Multiple Gestations -
Wickham

PROGRESS

(79 10 - 80 09) The protocol is completed and a manuscript is in preparation. Suppression of maternal cortisol was apparent 24 hours after betamethasone treatment. In 4 of 7 ewes the stress of surgery was enough to over-ride pituitary-adrenal suppression as manifest by the mild rise in post-operative cortisol levels. Cord blood (fetal) cortisol was undetectable in treated twin and singleton lambs. Neither the L/S ratio nor pulmonary compliance showed a direct relationship with either twin gestation or increasing betamethasone dose. There was significant improvement in compliance with steroid treatment of premature singletons but no further significant changes with twin gestation or increased steroid dose. This supports data reported in human trials. The most interesting findings were the consistent intra-group differences between twins for L/S ratios and lung compliance. The explanation for this difference is not clear.

STATUS: (C)

TITLE: Comparison of Capillary (Heelstick) and Central (Venous) Total White Blood Cell Counts and Differentials in Normal Newborn Infants

PRINCIPAL INVESTIGATOR: CPT Bruce E. Willham, MC

PROFESSIONAL ASSISTANTS: COL Errol R. Alden, MC
MAJ Amil Ortiz, MC
MAJ Lawrence Wickham, MC
CPT Michael Byrne, MC

WORK UNIT NO: 79/82

TECHNICAL OBJECTIVE

To determine if a statistically significant difference exists between total white blood cell counts and differentials in blood samples obtained from normal healthy newborns during the first 24 hours after birth by heelstick and by venous sampling from peripheral veins. This will define the "normal" standards and provide a basis for evaluation of "sick" newborns.

METHOD

Simultaneous blood samples by heelstick and by venipuncture will be taken and standard methods will be used to determine total WBC and differentials. Whenever possible the sampling will coincide with and compliment sampling performed for routine purposes. Data will be analyzed using the paired t statistic to determine if the peripheral WBC differ from the central WBC. Also, regression analysis of the data will be performed to evaluate associations of central and peripheral counts.

PROGRESS

(80 04 - 80 09) The implementation of this protocol was delayed due to lengthy approval procedures and reassignment of several of the investigators. However, the protocol has now begun with testing of several infants.

STATUS: (0)

TITLE: Comparison of Five Physical Medicine Treatment Approaches for Shoulder Bursitis, Tendonitis, and Lateral Epicondylitis of the Elbow

PRINCIPAL INVESTIGATOR: MAJ Mohammad A. Saeed, MC

PROFESSIONAL ASSISTANTS: MAJ Ronald J. Franklin, AMSC
1LT John S. Halle, AMSC
2LT Barry L Karalfa, AMSC

WORK UNIT NO: 80/41

TECHNICAL OBJECTIVE

In an effort to obtain better symptomatic patient relief, the Physical Medicine Service at Madigan has designed five distinct treatment protocols for the subject disorders. The purpose of this study is to quantify the effectiveness of these treatment procedures.

METHOD

One hundred patients clinically identified as having either shoulder bursitis or tendonitis of the shoulder or elbow will be randomly assigned to one of five treatment categories: (1) ultrasound with coupling agent; (2) ultrasound with hydrocortisone coupling agent; (3) TENS with coupling agent; (4) TENS with hydrocortisone coupling agent; and (5) injection with lidocaine and hydrocortisone. All of these treatment programs also include identical home exercise regimes and ice treatment. Prior to treatment, each patient's pain will be assessed by the McGill pain questionnaire. Following a five day treatment period, each patient will again assess his pain by repeating the questionnaire. The data will be analyzed by the Matched Student's t Test and a Two-Way Analysis of Variance.

PROGRESS

(80 05 - 80 09) Data on 15 subjects has been collected. One treatment group (#2) was deleted from this study because the hydrocortisone cream used in conjunction with ultrasound was found to have poor iontophoretic properties when used with the transcutaneous electrical nerve stimulators.

Comparison of Five Physical Medicine Treatment Approaches -
Saeed

Data collection has been slower than anticipated for several reasons. One problem is that the potential participant has to agree to come in for treatment on five consecutive work days, which not all potential subjects are willing or able to do. An unexpected difficulty is the language barrier created with those individuals who speak English as a second language. The assessment tool relies heavily on an understanding of "descriptor words" and individuals that were originally raised in another country have repeatedly had problems understanding these terms. These problems coupled with the frequent occurrence of a potential participant with other multiple medical problems that could cloud the results, have slowed the data collection. The investigators plan to continue data collection until 100 questionnaires are completed and then to analyze the date.

STATUS: (0)

TITLE: The Effects of Low Exposure Levels to Anesthetic Gases in Operating Rooms at MAMC

PRINCIPAL INVESTIGATOR: CPT Robert R. Byland, MSC

PROFESSIONAL ASSISTANTS: LTC John Heggers, MSC
MAJ George S. Ward, VC
CPT Michael Smith, MSC
CPT Gary L Shrum, MSC

WORK UNIT NO: 77/72

TECHNICAL OBJECTIVE

To evaluate the levels of anesthetic gas the anesthesiologist and operating room personnel receive with the present type of gas delivery, recovery, and disposal systems used at this center.

METHOD

1. Coordinate with OR supervisor and anesthetist as to the length of time various operations take and the gases used.
2. Schedule twelve operations to test for gases.
3. Use previous ventilation survey results for room volume and air turnover rate to predict gas concentrations.
4. Determine prior to any operation the effect of opening and closing of OR doors has on the air flow.
5. Set up the Miran I.R. unit and calibrate.
6. Using the 10-foot sampling hose, collect samples during the operation.
7. Samples will be collected around gas delivery systems, the anesthesiologist, and OR personnel's breathing zones.
8. Samples will be collected every 15 minutes and recorded on a strip chart.
9. Analysis of collected data.

The Effects of Low Exposure Levels to Anesthetic Gases in
Operating Rooms at MAMC - Byland

PROGRESS

(79 10 - 80 09) During FY 80, three series of ventilation measurements and waste anesthetic gases monitoring sessions were accomplished. Hopefully, more time can be devoted to this project in the future if trained personnel resources increase.

Due to the departure of CPT Byland, CPT Gary L. Shrum will assume the duties of principal investigator on this protocol.

STATUS: (0)

TITLE: Estimation of Exposures of Premature Infants to Ionizing Radiation, Primarily From X-Ray Sources.

PRINCIPAL INVESTIGATOR: 1LT John H. Pickering, MSC

PROFESSIONAL ASSISTANT: SFC Joseph H. Smith

WORK UNIT NO: 80/49

TECHNICAL OBJECTIVE

To evaluate whole body exposures to premature infants and relate the estimates to threshold damage of various tissue and/or organs.

METHOD

The investigators will survey the x-ray source used for these infants and determine the skin entrance exposure with the techniques used by the x-ray department. A sheet will be attached to the beds of the infants and the x-ray technician will indicate the number of exposures taken of a particular infant. Film badges will be placed with the infants on a random basis to estimate scatter radiation from adjacently exposed patients.

PROGRESS

(80 06 - 80 09) This project has been delayed for several months until expected manpower resources arrive.

STATUS: (0)

TITLE: Study of Marital Adjustment as It Relates to the
Retention of Military Medical Personnel

PRINCIPAL INVESTIGATOR: MAJ Larry Sanderlin, MSC

PROFESSIONAL ASSISTANTS: LTC Jerry L. McKain, MSC
Barbara L. Fisher, Ph.D.
Charles York, M.S.W.

WORK UNIT NO: 79/87

TECHNICAL OBJECTIVE

To examine systematically the relationship between peer popularity and marital satisfaction variables as these relate to military career decisions of Army Medical Department personnel.

METHOD

Initial data collection will be two paper and pencil instruments. The first is a well known instrument which measures marital adjustment (Spanier, 1976). The second is being developed specifically for this type of research. To establish the validity of this instrument, a standardized research procedure will be used by comparing clinic and non-clinic families. This data would provide norms for the friendship instrument and establish its validity for the final phase of the project. The final phase will include at least 10 couples (ideally 20 couples) who are active duty 91C students and their spouses. They will complete the marital and friendship adjustment questionnaires. Some demographic data will also be requested. A sociometric instrument would also be utilized to measure actual friendship formation within this group. Data analysis will include statistical procedures to establish the reliability and validity of the instruments used. The sociometric data on the 91C group will also provide a second statistical measure of instrument validity. Statistical procedures will be utilized to assess the relationship between marital adjustment and friendship adjustment as an indicator of an individual's overall adjustment to his contextual relationships.

PROGRESS

(79 10 - 80 09) This protocol was terminated due to a lack of funding from HSC.

STATUS: (T)

TITLE: Implantation of Intraocular Lenses

PRINCIPAL INVESTIGATOR: LTC Stanley C. Allison, MC

PROFESSIONAL ASSISTANTS: COL Stanley C. Sollie, MC
LTC Christopher G. Knight, MC
MAJ Bruce D. Bellin, MC
CPT Lawrence E. Hannon, MC
LTC John C. Goodin, MC

WORK UNIT NO: 79/64

TECHNICAL OBJECTIVE

To become proficient in intraocular lens implantation and to gain investigator status with FDA requirements, thereby providing a new technique in ophthalmic surgical care for our patients.

METHOD

1. Obtain appropriate instruments to accomplish the procedure.
2. Obtain research investigator status with companies that have FDA approval to supply the lenses.
3. Implant lenses in 10 rabbits as a training experience for surgical nurses and assistants in this procedure.
4. Implant lenses in appropriately selected patients in order to provide visual rehabilitation.
5. To eventually establish this as a routine procedure in the military medical armamentarium of ophthalmic care.

PROGRESS

(79 10 - 80 09) Twenty intraocular lens implantations have been done, and the investigators plan to continue these implantations indefinitely.

Due to the departure of LTC Allison, COL Stanley Sollie has assumed the duties as principal investigator of the protocol

STATUS: (0)

TITLE: A System for Data Storage and Retrieval Using a Microcomputer: Carcinoma of Prostate Patients, Madigan Army Medical Center

PRINCIPAL INVESTIGATOR: COL Alfred S. Buck, MC

PROFESSIONAL ASSISTANTS: LTC William D. Belville, MC
LTC Martin L. Dresner, MC
MAJ Willis H. Jacob, MSC
MAJ Roger H. Schoenfeld, MC
CPT Carl F. Cricco, MC
CPT Robert U. Finnerty, MC

WORK UNIT NO: 80/36

TECHNICAL OBJECTIVE

To test the concept of a microcomputer-based system for storage and processing of patient records.

METHOD

The population selected for this study are all patients with carcinoma of the prostate seen at Madigan. A systems analyst will review the data and develop a program which will be designed to permit the following: (1) open file on patient; (2) update data in the file; (3) retrieve the complete file; (4) retrieve a single category of data (variable) from the file of one or more patients; and (5) retrieve a single category of data (variable) from two or more groups of patients and perform the required statistics for comparisons between the groups. The system will be evaluated after it has been operational for six months. If the program is found to be workable, it will be turned over to the Automation Management Office for implementation.

PROGRESS

(80 04 - 80 09) Various data requirements and existing computer entry summary sheets have been reviewed. The requirements of the program have been given to an analyst in the Automation Management Office for his review and recommendations.

STATUS: (0)

TITLE: "Ball and Socket" Interphalangeal Joint Arthrodesis

PRINCIPAL INVESTIGATOR: COL Richard A Camp, MC

PROFESSIONAL ASSISTANT: MAJ Michael H. Callahan, MC

WORK UNIT NO: 80/45

TECHNICAL OBJECTIVE

To conduct a retrospective review of the experience of Madigan Orthopaedic Service with interphalangeal joint arthrodesis of the hand and foot using the MIRA MARK II finger joint reamers.

METHOD

The investigators will review the inpatient charts, outpatient records, and x-rays of the patients who have undergone interphalangeal joint arthrodesis using the MIRA MARK II finger joint reamers. Data will be analyzed and a paper will be prepared if data are significant.

PROGRESS

(80 06 - 80 09) The protocol is completed. The results show a very high rate of fusion (96%) was obtained with minimal inconvenience to the patient. A manuscript is in preparation. An abstract has been submitted and accepted for presentation at the 44th Annual Meeting of the Western Orthopaedic Association, 23 Oct 80, Honolulu, HI.

STATUS: (C)

TITLE: The Effect of Dimethyl Sulfoxide on the Uptake of Thio-TEPA From the Urinary Bladder of the Dog

PRINCIPAL INVESTIGATOR: CPT Carl F. Cricco, MC

PROFESSIONAL ASSISTANTS: MAJ Eduardo S. Blum, MC
MAJ Willis H. Jacob, MC
MAJ George S. Ward, VC

WORK UNIT NO: 79/57

TEHCNICAL OBJECTIVE

Thio-TEPA has been used in the management of various types of neoplasias for almost two decades. However, its use in the management of urinary bladder carcinoma has had mixed results. In addition, the cytotoxic effects of thio-TEPA on the hematopoietic tissues are a severe side effect in its use. The objective of this study is to determine if intravesicular thio-TEPA can be more effectively transported through the urinary bladder wall using DMSO as a carrier.

METHOD

Ten dogs will be divided into groups I and II (4 dogs each) and Group III (2 dogs). The test solution (50 ml) will be instilled into the urinary bladder of each animal and maintained there for one hour. The test solutions are: Group I - 45 mg thio-TEPA in 50% DMSO; Group II - 45 mg thio-TEPA in an isotonic salt solution; and Group III - 50% DMSO in an isotonic salt solution. The Group III animals are to verify that DMSO does not interfere with thio-TEPA identification.

Blood samples will be obtained from the caudal vena cava and the external jugular vein immediately before instillation of the test solution and at 5, 10, 20, 40, and 60 min after instillation. One blood sample will be taken from a small vein on the bladder surface at 15 min and the test solution will be withdrawn from the bladder at 60 minutes.

Two dogs from Groups I and II will be studied for toxicity following a complete treatment regime, consisting of four weekly treatments as described above. These animals will have bone marrow, liver, kidney, and spleen biopsies before the first treatment. One week following the last treatment, the dogs will be sacrificed and tissue sections of the same

The Effect of Dimethyl Sulfoxide - Cricco

organs plus the urinary bladder and lens will be taken. These tissues will be examined histopathologically for evidence of toxic changes. Complete blood counts will also be performed at weekly intervals.

The remaining two dogs in Groups I and II will have a section of urinary bladder removed following the test solution instillation. This tissue section will be divided and one part homogenized and extracted for thio-TEPA analysis and the other section evaluated histopathologically.

The withdrawn test solution, blood samples, and bladder tissue extracts will be analyzed by spectrophotometry to determine levels of thio-TEPA. The results will be compared to determine effectiveness of DMSO in increasing absorption of thio-TEPA.

PROGRESS

(79 10 - 80 09) Progress on this protocol has been hampered by the difficulty in developing a suitable assay for Thio-TEPA. Initial efforts to develop a spectrophotometric assay for Thio-TEPA failed because of the low sensitivity of the assay. Subsequent attempts to use a gas chromatographic procedure also failed. Thio-TEPA has been set aside until a high pressure liquid chromatograph becomes available. 5-fluorouracil is now being investigated and progress is being made in developing a gas chromatographic assay for this agent. Cis-Platinum will be studied after the series using 5-fluorouracil has been completed.

Due to the departure of CPT Cricco, CPT Robert Finnerty, MC, has assumed the duties as principal investigator of the project.

STATUS: (0)

TITLE: Bulbocavernosus Reflex and Conduction Velocity of Dorsal Penile Nerve in Normal Men

PRINCIPAL INVESTIGATOR: COL Martin L. Dresner, MC

PROFESSIONAL ASSISTANT: MAJ Mohammad A. Saeed, MC

WORK UNIT NO: 80/67

TECHNICAL OBJECTIVE

To determine the normal values of the bulbocavernosus reflex arc as transmitted through the dorsal penile nerve as an indicator of peripheral neuropathy. Peripheral neuropathy is one of the causes of organic impotence.

METHOD

Approximately 25 men will be studied with electrophysiological testing of the bulbocavernosus reflex to determine reflex latency and conduction velocity of the dorsal penile nerve. Subjects will have no history or clinical evidence of any disorder which would affect the peripheral nervous system and sural nerve conduction will be tested to rule out subclinical peripheral neuropathy. A monopolar teflon coated needle electrode will be placed in either the right or left bulbocavernosus muscle and the dorsal penile nerve will be stimulated with bipolar stimulator electrode at the base of the penis and the glans penis using TECA TE4 electromyogram. These stimuli will be delivered with a frequency of 1/second and a pulse duration of 0.5 msec. At least five identical responses will be recorded. Motor unit action potential of bulbocavernosus muscles, recruitment pattern in bulbocavernosus muscles, reflex latency, wave form, and dorsal penile nerve conduction velocity will be evaluated.

PROGRESS

(80 07 - 80 09) Of the 55 patients ... the bulbocavernosus reflex was abnormal in 11 patients when the stimulation was done at the base of the penis. The number of abnormal reflex studies increased to 15 patients when the stimulation was done at the glans penis. The range of the bulbocavernosus reflex was from 25 msec to 100 msec. More patients will be studied.

STATUS: (0)

PRESENTATION: Singh, S., Dresner, M., and Saeed, M.: Bulbocavernosus Reflex in Men with Impotence. Amer Assoc of Electromyography & Electrodagnosis, 26 Sep 80.

TITLE: An Evaluation of the Safety and Efficacy of Cyanoacrylate Ester in Ossicular Reconstruction and Nerve Graft Anastomosis in the Guinea Pig Middle Ear

PRINCIPAL INVESTIGATOR: COL William H. Gernon, MC

PROFESSIONAL ASSISTANT: CPT Roy Kim Davis, MC

WORK UNIT NO: 77/88

TECHNICAL OBJECTIVE

To determine the safety and efficacy of cyanoacrylate ester in the middle ear; specifically, for ossicular reconstruction for histological changes in the oval window area and in the facial nerve. In addition, the use of this compound in tympanoplasty would be a natural extension of this project. The intended purpose of this study is to open the door for the use of cyanoacrylate ester in human surgery, initially on an experimental basis.

METHOD

The investigators propose to use Histoacryl and Crazy Glue to do interpositions (incus) on a test group of guinea pigs as well as place glue on the facial nerve, perhaps to do facial nerve anastomoses, and to place the glue in the oval window area. Approximately 39 animals would be utilized. At 3, 6, and 12 months, 12 experimental animals and one control animal would be sacrificed. Histological temporal bone studies would then be conducted at AFIP.

PROGRESS

(79 10 - 80 09) To date, approximately 18 guinea pigs have undergone surgical exploration of their ears with the use of cyanocrylate to fix the ossicles in the bulla and to be used in facial nerve anastomosis after transection. Nine animals have been sacrificed and their skulls are being processed at AFIP to determine the pathologic effects of this tissue glue. Processing takes 8-12 months. Depending on these results, further procedures may be carried out in the area of nerve grafting. The remaining animals will be sacrificed in the next three to six months.

STATUS: (0)

TITLE: Medical Treatment of the Frey Syndrome

PRINCIPAL INVESTIGATOR: COL Leonard L. Hays, MC

PROFESSIONAL ASSISTANT: Alvin J. Novack, M.D.
University of Washington

WORK UNIT NO: 76/06

TECHNICAL OBJECTIVE

1. To study objectively the true incidence of the Frey Syndrome in post-parotidectomy patients by means of the Minor Starch Iodine Test.
2. To determine the effect of, and patient satisfaction with, medical management comparing on a double blind basis topical use of a placebo, varying concentrations of scopolamine hydrobromide, and the newer anticholinergic agent, glycopyrrolate.
3. To investigate the value and practicality of iontophoresis of the above agents to increase the duration of satisfactory control of sweating.
4. To compare the topical use of a patient's most effective antiperspirant on the involved facial skin with the result from the topical use of the most effective agent in the double blind series for that patient.

METHOD

Phase I - Double-blind treatment with 1%, 1%, and 3% scopolamine hydrobromide cream, 0.1% glycopyrrolate, and a placebo; comparison by the patient as to effectiveness; and retreatment after drug dosage adjustment if the patient fails to respond.

Phase II - Utilize iontophoretic introduction of the best anticholinergic agent to a group of volunteers with significant sweating symptoms and to a group who are medical failures and compare action and duration of action with iontophoretic introduction using tap water, Ringer's lactate, or saline.

Medical Treatment of the Frey Syndrome - Hays

Phase III - Patients who failed medical treatment or have become dissatisfied with the medical treatment and have significant symptoms confirmed on minor starch-iodine testing will be offered surgery such as flap elevation or tympanic neurectomy.

PROGRESS

(79 10 - 80 09) The topical use of a 1/2 and 1% roll-on or a vanishing cream based preparation in the same concentration has continued to prove effective and safe to control the Frey syndrome. There have been no significant side effects to date. The data provided in previous reports remain valid. Approximately ten patients have continued to use the medication on an as desired basis.

STATUS: (0)

PUBLICATION: Hays, L.L.: The Frey Syndrome: A Review and Double Blind Evaluation of the Topical Use of a New Anticholinergic Agent. Laryngoscope 88:1796-1824, 1978.

SOUTHWEST ONCOLOGY GROUP PROTOCOLS

PRINCIPAL INVESTIGATOR:

LTC FRIEDRICH H. STUTZ, MC

PROFESSIONAL ASSISTANTS:

SURESH KATAKKAR, M.D., DAC

LTC Irwin Dabe, MC

TITLE: Teaching Program for Practical Microsurgery

PRINCIPAL INVESTIGATOR: MAJ Robert Kenevan, MC

PROFESSIONAL ASSISTANTS: COL Leonard L. Bays, MC
LTC Darin Holland, MC
MAJ Stanley Jackson, MC
MAJ George S. Ward, MC

WORK UNIT NO: 7/92

TECHNICAL OBJECTIVE

To establish a formal training program at Madigan Army Medical Center in clinical microsurgery.

METHOD

The teaching program will be established at the Department of Clinical Investigation, and a room will be set aside for the project where equipment for the microsurgery can be housed. A schedule of two afternoons per week will be set aside for teaching sessions. Animal model preparations (cadaver and live) will be developed by the veterinary surgical consultant with the support of the clinical teaching staff. Sessions will begin with lectures, followed by practical exercises in anatomy and step-by-step instruction in the surgical techniques.

PROGRESS

(74-10 - 86-09) Twenty-nine (29) microvascular teaching sessions have been performed during the past 12 months to maintain and develop skills. Staff members from Otolaryngology, Microsurgery, Orthopaedics, and Plastic Surgery have participated.

Due to the reassignment of MAJ Kenevan, LTC Thomas G. Griffith, MC, has assumed the duties of principal investigator for this protocol.

STATUS: (N)

TITLE: Lid Magnets for Correction of Orbicularis Palsy

PRINCIPAL INVESTIGATOR: COL Stanley C. Sollie, MC

PROFESSIONAL ASSISTANTS: MAJ Kurt Guelzow, MC
MAJ Frederick A. Mausolf, MC

WORK UNIT NO: 75/27

TECHNICAL OBJECTIVE

To study the effects of the insertion of lid magnets on the tarsal plates of the lids involved in seventh nerve palsy.

METHOD

Patients with seventh nerve palsy will be evaluated, and, if the palsy persists longer than six months without showing improvement and if the eye is affected by the lack of lid closures, these patients will be considered for the surgery. The surgery consists of implanting lid magnets, supplied through Wolfgang D. Muhlbauer, Department of Plastic and Reconstructive Surgery, Klinikum rechts der Isar of the Technical University, Munich, Germany. A skin incision is made in the upper and lower lid and the magnets are sutured to the tarsus. The skin incision is then closed.

PROGRESS

(79 10 - 80 09) No additional lid magnets were implanted in FY 80. All of the patients in the study who are in the area were examined and have remained free of complications. A manuscript is in preparation for submission for publication.

STATUS: (0)

TITLE: An Analysis of the Prevalence, Severity, and Correlates of Drug and Alcohol Abuse at a Large Army Installation

PRINCIPAL INVESTIGATOR: John P. Allen, PhD, DAC

PROFESSIONAL ASSISTANT: None

WORK UNIT NO: 78/21

TECHNICAL OBJECTIVE

To provide answers as to the availability of illicit drugs (both on post and in the civilian community); the incidence and nature of illicit drug and alcohol abuse at Fort Lewis and Madigan Army Medical Center; the relationship of substance abuse to social climate, authority relationships, and military preparedness; the relationship to rank, demographic characteristics, abuse-nonabuse characteristics of individuals, etc.; the relationship of alcohol abuse and drug abuse; what characteristics observable by commanders and supervisors define high risk individuals; the psychological/demographic correlates of alcohol-related offenses; the effectiveness of urinalysis as a deterrent; to what groups the ADAPCP can most effectively address its educational/preventive aspects; and what concrete, feasible and promising suggestions can be made to reduce local and Army-wide problems with drug and alcohol abuse.

METHOD

Sample population will be randomly selected across military ranks on the basis of SSN's and will consist of approximately 3,000 soldiers. After appropriate training, the survey will be administered by battalion adjutants. Data will be submitted to a broad range of correlational and multivariate analyses and will attempt to provide information as stated in the objective section above. Considerable effort will be expended both in data interpretation and in exploration of the preventive health care implications of these statistical analyses. After interpretation of statistical analyses and formulation of action suggestions, the results and proposed course of action will be submitted to Headquarters, 9th Infantry Division and Madigan Army Medical Center (and, if appropriate, to OTSG, HSC, and other higher headquarters). Appropriate information will be disseminated to major subordinate commanders and Alcohol and Drug Dependency Intervention Council.

An Analysis of the Prevalence, Severity, and Correlates of
Drug and Alcohol Abuse at a Large Army Installation - Allen

PROGRESS

(79 09 - 80 09) The survey demonstrated that while no relationship between substance abuse and demographic correlates could be found for officers, age, sex, education, rank, years in service, and occupation were significantly associated with both drug and alcohol abuse among enlisted personnel.

The study measured the relationships between drug abuse, alcohol abuse, and concurrent drug and alcohol abuse with three dimensions of military morale; task satisfaction, perceived combat readiness, and interpersonal relationships. Among Army officer personnel and among enlisted personnel who engage only in drug abuse, no relationship was found. Alcohol abuse alone and concomitant drug and alcohol abuse among enlisted are associated with a lower sense of task satisfaction and perceived combat readiness even when the effects of sex, age, rank, education, and years in service on substance abuse are eliminated. The study suggests that those enlisted who engage in both drug and alcohol abuse are higher in interpersonal relationships or camaraderie than those who do not.

Three papers have been submitted for consideration for publication from this project.

STATUS: (C)

TITLE: M-77-1, Forty-Two Hour Methotrexate Infusions with Citrovorum Rescue - A Clinicopharmacokinetic Analysis (A Phase I-II Study).

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/48

TECHNICAL OBJECTIVE

To determine the maximal tolerated dose of methotrexate (MTX) which will maintain a constant plasma antifolate concentration for 42 hours.

To identify what clinical factors alter renal clearance of MTX.

To evaluate the antitumor effect of 42-hour MTX infusions with citrovorum.

METHOD

Patients with any cancer resistant to conventional therapy who meet the other criteria as outlined in the protocol will enter the study in sequence, four patients being treated at each plasma MTX level as outlined in the protocol. A course of treatment will consist of a priming dose of MTX over the first hour, an infusion of MTX over the subsequent 41 hours, and citrovorum factor rescue thereafter, beginning at the time MTX is discontinued. Courses are repeated every two weeks.

At Madigan Army Medical Center this treatment is being used only in patients with tumors that have shown response to it, e.g., sarcoma.

PROGRESS

(77 08 - 80 09) This protocol is completed. No patients were entered during FY 80. Previously two patients had been entered. One has died; the other was still alive 20 months after treatment but has been lost to follow-up in recent months.

STATUS: (C)

TITLE: SWOG 781, Phase III Protocol - Radiotherapy-Chemotherapy (MOPP) for Stages I and II, A and B Hodgkin's

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/55

TECHNICAL OBJECTIVE

To compare total nodal radiotherapy (TN-XRT) or "mantle" and para-aortic radiotherapy to involved field radiotherapy (IF-XRT) plus MOPP (nitrogen mustard, vincristine, prednisone, and procarbazine) chemotherapy in patients with stages I and II, A and B disease.

METHOD

Patients with biopsy-proven Hodgkin's disease who have received no prior chemotherapy or radiotherapy and who meet other criteria as outlined in the protocol will be randomized to one of two treatment programs: (1) TN-XRT; (2) IF-XRT followed by MOPP chemotherapy. Following completion of the IF-XRT, a rest period of four weeks will be interposed before chemotherapy is started. Dosages for chemotherapy and radiotherapy and length of courses of treatment as specified in the protocol.

PROGRESS

(77 08 - 80 09) No patients have been registered on this protocol. The protocol is now closed.

STATUS: (..)

TITLE: SWOG 7426/27, Chemoimmunotherapy for the Non-Hodgkin's Lymphomas. CHOP-Bleomycin vs CHOP + BCG vs COP + Bleomycin Induction Therapy. No Maintenance vs BCG for Maintenance

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/41

TECHNICAL OBJECTIVE

1. To compare the effectiveness of two chemotherapy regimens (CHOP + bleomycin) or chemoimmunotherapy (CHOP + BCG) for remission induction in previously untreated patients with non-Hodgkin's lymphomas.
2. To establish baseline and serial data on immunologic status in both chemotherapy and chemoimmunotherapy groups.
3. To evaluate systematic restaging of patients judged to be in complete clinical remission (CR).
4. For patients proven to be in complete remission after induction, to test the value of continued maintenance immunotherapy (BCG) vs no maintenance treatment.
5. For patients who only achieve a partial remission during induction, to test the effectiveness of continued treatment with chemoimmunotherapy.

METHOD

Patients with any histologic type of stage III or IV non-Hodgkin's lymphoma established by biopsy will be randomized to one of the three induction programs. The schema for the study is given in the protocol. Remission Induction: Eight courses of treatment will constitute remission induction. If induction results in a CR and this is confirmed by restaging, then the patient is eligible for a second randomization into the maintenance phase of this study. If residual lymphoma is detected during restaging, an additional three courses of treatment will be administered, restaging repeated, and patients in CR will be eligible after 11 courses of induction for the maintenance phase. Patients who are only in a partial remission after 11 courses of treatment are eligible for continued treatment with chemoimmunotherapy.

SWOG 7426/27 - Stutz

PROGRESS

(77 03 - 80 09) One patient was entered on the protocol in July 1977 with good partial remission; died June 1979. This protocol is now closed.

STATUS: (C)

TITLE: SWOG 7433, Non-Hodgkin's Lymphomas (Stage I, I_E , II and II_E). A Phase III Study

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/53

TECHNICAL OBJECTIVE

To compare the remission rate, remission duration and survival in patients with non-Hodgkin's lymphoma, pathologic stages I, I_E , II and II_E treated with extended field radiotherapy (supra-diaphragmatic mantle or abdominal field) alone or with extended field radiotherapy plus combination chemotherapy (Cytoxan, Hydroxyl-daunorubicin(adriamycin), Oncovin (vincristine), and prednisone).

METHOD

Patients newly diagnosed (no type of prior therapy) with non-Hodgkin's lymphoma except mycosis fungoides and diffuse lymphocytic well differentiated lymphoma will be thoroughly evaluated for extent of disease and then randomized to either radiation therapy or radiation therapy plus chemotherapy. If the patient does not achieve a complete remission after completion of his treatment course, he will be removed from the study. Those achieving complete remission will be followed for two years or until relapse.

PROGRESS

(77 08 - 80 09) One patient was entered during FY 80 but was ineligible because of bone marrow involvement found at a later date; patient is alive and in remission. One patient was treated from May 1978 to November 1978; in complete remission on last follow-up in September 1980.

STATUS: (0)

TITLE: SWOG 7440, Adjuvant Chemotherapy for Osteogenic Sarcoma

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/17

TECHNICAL OBJECTIVE

1. To determine the efficacy of combination chemotherapy with CY-VA-DIC (cyclophosphamide, vincristine, adriamycin, and DIC) in preventing the development of metastases in patients with osteogenic sarcoma who have received definitive surgery for their primary lesions and who have no evidence of residual disease.
2. To determine the survival and disease-free interval pattern of patients on this study to be compared to historic controls in the medical literature.

METHOD

Patients with a confirmed diagnosis of osteogenic sarcoma who have received definitive surgical therapy and have no evidence of metastases following surgery and who have not received any prior therapy (other than surgery) shall be treated with a chemotherapy regimen consisting of vincristine, adriamycin, cyclophosphamide, and DIC as outlined in paragraph 5.0 of the protocol.

PROGRESS

(% 12 = 39.09) No patients have been entered on this protocol. The study is now closed.

STATUS: (C)

TITLE: SWOG 7510, Intensive Adjuvant Chemotherapy with or without Oral BCG Immunotherapy for Patients with Locally Advanced Adenocarcinoma of the Large Bowel

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/18

TECHNICAL OBJECTIVE

To determine the efficacy of adjuvant chemotherapy with the highly effective combination of Methyl CCNU (MeCCNU) and 5-Fluorouracil (5-FU) and to determine whether this is added to or immunotherapy with oral Bacillus Calmette-Guerin (BCG) on the disease-free interval and survival of patients with Duke C large bowel adenocarcinoma.

METHOD

Patients will be randomly assigned to either of the two following regimens:

Chemotherapy alone - Methyl CCNU, given orally on day 1, plus intravenous 5-Fluorouracil, given intravenously weekly for three doses would constitute one course. Courses would begin every eight weeks.

Chemotherapy plus immunotherapy - Chemotherapy as described above plus immunotherapy in the form of oral BCG given every two weeks.

PROGRESS

(76 12 - 80 09) Eleven (11) patients are now on study and they are currently being followed for possible recurrence. The range of treatment varies from 48 months to 4 months. As of 1 Oct 80, no patients have shown evidence of recurrence.

STATUS: (0)

TITLE: SWOG 7517, Therapy of Squamous Cell Carcinoma of the Head and Neck Using Combination Bleomycin, Vincristine, and Methotrexate

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/26

TECHNICAL OBJECTIVE

To determine the toxicity and effectiveness of various dosage levels of a combination of bleomycin, oncovin, and methotrexate in the treatment of patients with squamous cell carcinoma of the head and neck.

METHOD

A total of thirty patients with squamous cell carcinoma of the head and neck will be treated with a combination of bleomycin, vincristine, and methotrexate as outlined in the protocol. Patients must receive two complete cycles of therapy to be evaluable for response. The duration of response shall be measured from the time that a partial response is achieved to the time at which progression is apparent.

PROGRESS

(7/ 09 - 3/ 09) No patients have been registered on this protocol. The protocol is now closed.

STATUS: (C)

TITLE: SWOG 7518, Stage III A and B Hodgkin's Disease Remission Induction by Radiation Therapy Plus Chemotherapy Combination versus Chemotherapy Alone. Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/52

TECHNICAL OBJECTIVE

1. To compare the effectiveness of 10 courses of a five-drug combination chemotherapy (including nitrogen mustard, vincristine, procarbazine, prednisone, and bleomycin) program against the combined three courses of chemotherapy followed by total nodal irradiation therapy program for complete remission induction in patients with Stage III asymptomatic -A or symptomatic -B disease.
2. To evaluate the systematic "restaging" of patients in apparent complete remission.
3. To assess the length of unmaintained remission after intensive induction with ten courses of chemotherapy treatment versus the combination chemoradiation therapy, after documentation of complete remission status by careful "restaging".
4. To assess the toxicity of the chemotherapy alone portion of the study versus the toxicity of the combination of chemotherapy and radiation therapy.
5. To intercompare the results of this program with those to be obtained by SWOG 7406 (ongoing).

METHOD

Patients with any histopathologic type Stage III Hodgkin's disease and no prior chemotherapy or radiation therapy who meet the other criteria as outlined in the protocol will be randomized to either Treatment 1 or Treatment 2. Treatment 1: chemotherapy alone (nitrogen mustard, vincristine, procarbazine, and prednisone plus bleomycin). Treatment 2: chemotherapy plus radiation therapy (chemotherapy as above followed by total nodal radiotherapy). At the completion of ten courses of chemotherapy or of the total combination chemotherapy, radiation therapy program, a thorough evaluation for evidence of persistent Hodgkin's disease is required. If complete remission is confirmed by this evaluation, no further treatment will be given until relapse occurs. If remission is not confirmed, appropriate treatment will be given on an individual basis.

SWOG 7518 - Stutz

PROGRESS

(77 08 - 80 09) No new patients were entered on this protocol during FY 80. One patient has been treated with complete remission; no evidence of disease three years after diagnosis; no evidence of disease 18 months after treatment was completed.

The study is now closed.

STATUS: (C)

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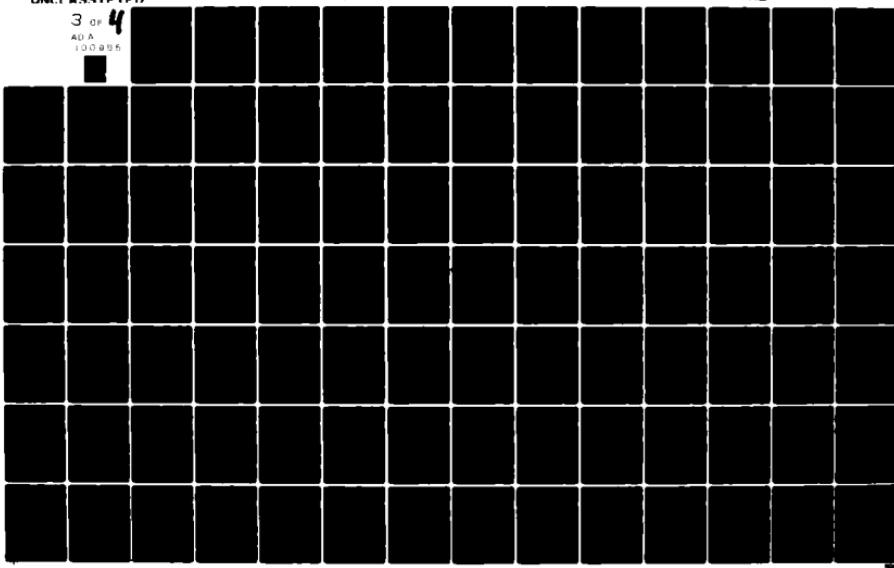
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NL



TITLE: SWOG 7521, Adjuvant Melanoma Protocol

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/38

TECHNICAL OBJECTIVE

1. To determine the efficacy of BCNU, hydroxyurea, and imidazole carboxamide (BHD) in preventing the recurrence of disease and prolonging the survival of patients with primary malignant melanoma who have received definitive surgical treatment for their primary lesions, have no evidence of residual disease, but in whom by the clinical and pathological characteristics of the primary lesion can be predicted to have a high incidence of recurrence. 2. To determine the efficacy of combination chemotherapy (BHD) with and without BCG in preventing the development of metastases and prolonging the disease-free interval and survival of patients with recurrent malignant melanoma which has been surgically excised ("minimal residual disease"). 3. To determine the immunocompetence of patients with malignant melanoma and any correlation with prognosis. 4. To determine the influence of chemotherapy and chemoimmunotherapy upon the immunocompetence of these patients with malignant melanoma.

METHOD

Patients who have a histologically confirmed diagnosis of malignant melanoma and have not been previously treated with chemotherapy or radiation therapy and meet the other criteria as outlined in the protocol shall be entered in the study. Patients will be classified as follows for randomization: Class I - localized disease; Class II - regional and solitary distant metastatic disease. Patients with Class I disease will be randomized between BHD and no treatment. Patients with Class II disease will be randomized to either BHD or BHD + BCG. Patients will be treated for one year or until recurrent disease develops. Patients randomized to no treatment will be followed in a similar fashion. After one year of treatment patients are to remain on study and be followed on no treatment.

SWOG 7521 - Stutz

PROGRESS

(77 01 - 80 09) No new patients entered during FY 80. One patient was randomized to the no treatment arm with recurrence after 11 months. A second patient received one course of treatment and refused further therapy secondary to side effects. Patient was alive and well three months after registration.

STATUS: (0)

TITLE: SWOG 7522, Chemotherapy, Splenectomy With or Without Immunotherapy in the Treatment of Chronic Myelogenous Leukemia. Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/78

TECHNICAL OBJECTIVE

To study the effects of chemotherapy, splenectomy, and/or immunotherapy on leukemic cytogenetics, immune status, appearance of blastic transformation, and any influence in overall survival.

a. To treat and control the early benign phase of chronic myelogenous leukemia with cytoxan, cytosine arabinoside, vincristine and prednisone and to study the influence of chemotherapy on bone marrow morphology, cytogenetics, and leukocyte alkaline phosphatase.

b. To study nonspecific cell mediated immunity prior to and following therapy.

c. To determine if immunotherapy with BCG will augment general immunocompetence of CML patients.

d. To remove extra tumor burden, avoid possible complication of splenic infarction and hypersplenism through surgical splenectomy.

METHOD

Splenectomy for patients entering this study will be elective. Within each group (splenectomy or no splenectomy) patients will be randomized to receive chemotherapy alone or chemotherapy + BCG immunotherapy. Hence, there will be four groups of patients.

Induction Treatment:

Treatment 1: Cytosar 100 mg/M² day x 5, subcutaneous
Oncovin 1.0 mg IV day 1
Cytoxan 500 mg/M² IV day 1
Prednisone 100 mg PO day x 5
Tice BCG scarification on days 8 and 15

Treatment 2: COAP only (same dosages as for Treatment 1)

Following three courses of induction treatment, patients will be evaluated for splenectomy. For patients not undergoing splenectomy, maintenance chemotherapy will be initiated. Splenectomy will be planned during days 21-28 after COAP #3, when the peripheral circulating WBC is between 5 and 20,000/mm³.

SWOG 7522 - Stutz

Maintenance Treatment

Treatment 1: Hydroxyurea PO in 4 divided dosages daily.
Dosage depends upon the WBC.
BCG weekly between hydroxyurea courses.

Treatment 2: Hydroxyurea PO in 4 divided dosages daily.

PROGRESS

(77 07 - 80 09) No new patients were entered during FY 80.
In previous years, two patients were entered but were not
evaluable due to early death.

The study is now closed.

STATUS: (C)

TITLE: SWOG 7603, Effect of Schedule on Activity of 5-Azacytidine
in Acute Leukemia. Phase III Protocol

PRINCIPAL INVESTIGATOR: LTC FRIEDRICH H. STUTZ, MC

WORK UNIT NO: 77/39

TECHNICAL OBJECTIVE

This study will compare the activity and toxicity of single dose vs continuous 5-day infusions of 5-azacytidine in patients with acute leukemia.

METHOD

Patients will be randomized to one of the following regimens:

1. Single day infusion of 750 mg/M^2 . 5-azacytidine will be given in 3 divided doses (250 mg/M^2 administered in 200 ml of Ringer's lactate solution over 2 hours) at 4 hour intervals (2 hours on therapy, 2 hours off therapy).
2. Five day infusion of $300 \text{ mg/M}^2/\text{day}$. 5-azacytidine will be administered in 4 divided doses in 200 ml Ringer's lactate solution as a continuous infusion over each 6 hour period. Each 6 hour dose should be prepared within 2 hours before use, and preferably immediately before administration.

Courses will be repeated at 3 week intervals unless the bone marrow cellularity remains less than 10%. The dosage of subsequent courses of 5-azacytidine will be based upon the patient's response to the previous course.

PROGRESS

(77 03 - 80 09) No new patients were entered on this protocol during FY 80. One patient had been studied earlier, but expired too early (after three days) for response. The study is now closed.

STATUS: (C)

TITLE: SWOG 7620, Treatment of Early Squamous Cell Carcinoma of the Head and Neck with Chemotherapy or Chemoimmunotherapy Following Initial Surgery and/or Radiotherapy

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/35

TECHNICAL OBJECTIVE

To determine if the disease-free interval and survival of patients in high risk categories of squamous head and neck cancer can be improved by adjuvant chemotherapy or chemoimmunotherapy after initial surgery, radiotherapy, or combination approach have resulted in no clinically evident disease. To accumulate immunologic data in treated and untreated patients with this malignancy.

METHOD

Patients will be registered and randomized after the reaction from the initial operative or radiotherapeutic intervention has settled and when they have achieved no clinically evident disease. The randomization process must be accomplished no later than three months after the completion of the surgery or irradiation. The tumor will be stratified into one of the four broad anatomic regions: oral cavity, larynx, pharynx, nasal cavity, and para-nasal sinuses. The control group will receive no further therapy after initial surgery and/or irradiation. The chemotherapy group will consist of methotrexate 12 mg/M² IM daily x 3 days every 21 days for one year. The chemotherapy-immunotherapy arm will consist of methotrexate 12 mg/M² IM daily x 3 days every 21 days for one year with BCG scarifications administered on day 8 and 14 for eight doses of BCG. Following eight doses, the BCG may then be administered on day 14 only and continued for the remainder of the year. BCG will not be applied to the neck.

PROGRESS

(77 09 - 80 09) No patients have been registered on this protocol. The study is now closed.

STATUS: (C)

TITLE: SWOG 7622, Combined Modality for Mycosis Fungoides --
Stage I (Phase II)

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/60

TECHNICAL OBJECTIVE

1. To compare the effectiveness of combined electron beam therapy and adjuvant chemotherapy vs electron beam therapy alone for patients with Stage I mycosis fungoides to determine the time to recurrence and to determine the percentage of recurrence.
2. To determine the effectiveness of adjuvant chemotherapy and survival patterns of such patients.
3. To determine the value of staging laparotomy in the management of mycosis fungoides.

METHOD

Patients who have two or more skin biopsies read as mycosis fungoides by a pathology panel and who meet other criteria as listed in the protocol will be randomized to receive electron beam therapy alone or electron beam therapy and adjuvant chemotherapy. Electron beam total body irradiation will be given via the Stanford Technique to a dose of 3000-5000 rads/40-60 days. Following the completion of electron beam therapy a rest period of four weeks is completed before chemotherapy is started. Chemotherapy will consist of: Cytoxan, 450 mg/M² IV on day 1 only; adriamycin, 30 mg/M² on day 1 only; vincristine, 1.4 mg/M² on day 1; prednisone, 100 mg orally for 5 days; and bleomycin, 2 units/M² IV 30" after vincristine on day 1. A total of 8 cycles at 3-week intervals will be delivered. Patients will be followed indefinitely or to a point of relapse.

PROGRESS

(77 03 - 80 09) No patients have been registered on this protocol.

STATUS: (0)

TITLE: SWOG 7625, Combination Chemotherapy for Advanced Sarcomas of Bone and Mesothelioma Utilizing Rubidazole and DIC (Dimethyl Triazeno Imidazole Carboxamide)

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/61

TECHNICAL OBJECTIVE

1. To determine the efficacy in terms of rate of response of combination chemotherapy with the 2-drug regimen RubiDIC (Rubidazole + DIC) in patients with metastatic sarcomas of bone and mesothelioma.
2. To determine the duration of remission and survival pattern of patients on this study and compare them with that of patients with metastatic bone sarcomas and mesothelioma on previous Southwest Oncology Group or M.D. Anderson Hospital protocols using adriamycin containing regimens.
3. To determine the toxicity of the regimen especially with regard to cardiac toxicity.

METHOD

Patients with a biopsy-confirmed diagnosis of bony sarcoma or mesothelioma with measurable metastases who have already received appropriate surgical therapy, who have not received prior adriamycin, daunorubicin, rubidazole, DIC, or BIC, and who meet other criteria as outlined in the protocol will be entered in the protocol on two treatments. Treatment I (adequate marrow reserve) will consist of rubidazole, 150 mg/M² IV on day 1 and DIC, 250 mg/M²/day IV on days 1-5 inclusive. Treatment II (inadequate marrow reserve) will consist of rubidazole, 120 mg/M² IV on day 1 and DIC, 200 mg/M²/day IV on days 1-5 inclusive. For both treatments, a complete cycle of chemotherapy shall be repeated every 22 days. Patients who remain in complete remission having received a total of two years of chemotherapy will have the chemotherapy discontinued, but will continue to be followed.

PROGRESS

(77 09 - 80 09) No patients have been registered on this protocol.

STATUS: (C)

TITLE: SWOG 7632, Combined Modality Protocol for Recurrent Breast Cancer, Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/63

TECHNICAL OBJECTIVE

1. To establish the survival of breast cancer patients when treating the first recurrence with a coordinated hormonal chemotherapeutic approach.
2. To determine the efficacy of a response to the antiestrogen Tamoxifen in predicting response to ablative surgery.
3. To correlate hormonal manipulations with estrogen and progesterone receptors where possible.

METHOD

First recurrence patients who have been surgically and/or radiotherapeutically treated with the intent of cure of their primary disease and who meet other criteria as outlined in the protocol will be divided into two groups. Group I (no prior castration) will receive Tamoxifen, 10 mg BID, followed by castration plus Tamoxifen. Responding patients will subsequently undergo adrenalectomy or hypophysectomy; nonresponding patients will receive chemotherapy. Group II (prior castration) will start on Tamoxifen. Responding patients will after relapse go directly to adrenalectomy or hypophysectomy; nonresponding patients will go directly to chemotherapy. Surgical guidelines and chemotherapy as outlined in protocol.

PROGRESS

(77 08 - 80 09) No new patients during FY 80. Two previous patients. (1) Was taken off protocol after four months because of rapidly progressive disease; died 5 months later. (2) Patient was treated for 18 months; taken off protocol because she refused oophorectomy (which was also not medically the best course). Patient doing reasonably well on other medication.

STATUS: (0)

TITLE: SWOG 7634, Evaluation of MeCCNU Plus B-2'-Deoxythioguanosine and Mitomycin-C Plus B-2'-Deoxythioguanosine in the Treatment of Refractory Disseminated Colorectal Carcinoma. Phase III Study

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/65

TECHNICAL OBJECTIVE

1. To evaluate the effectiveness of MeCCNU plus B-2'-deoxythioguanosine (BTGdR) for remission induction in disseminated colorectal carcinoma for patients failing to respond or relapsing from chemotherapy with Mitomycin-C plus 5-FU or Mitomycin-C plus Ftorafur, 5-FU alone, or Ftorafur alone.
2. To evaluate the effectiveness of MITO-C plus BTGdR for remission induction for patients failing to respond or relapsing from chemotherapy with MeCCNU plus 5-FU or MeCCNU plus Ftorafur, 5-FU alone, or Ftorafur alone.

METHOD

Patients with histologically proven disseminated colorectal carcinomas who meet the other criteria as outlined in the protocol will be treated as follows:

Treatment 1: Patients with prior exposure to MeCCNU + 5 FU or MeCCNU + Ftorafur, 5-FU alone or Ftorafur alone.

Good risk: MITO-C, 15 mg/M² IV days 1 and 56

BTGdR, 60 mg/M² days 1-5, 28-32, 56-60

Poor risk: MITO-C, 10 mg/M² IV on days 1 and 56

BTGdR, 50 mg/M² on days 1-5, 28-32, 56-60

Treatment 2: Patients with prior exposure to Mitomycin-C + 5-FU or Mitomycin + Ftorafur, 5-FU alone or Ftorafur alone.

Good risk: MeCCNU, 130 mg/M² PO on days 1 and 56

BTGdR, 60 mg/M² on days 1-5, 28-32, 56-60

Poor risk: MeCCNU, 100 mg/M² PO on days 1 and 56

BTGdR, 50 mg/M² on days 1-5, 28-32, and 56-60

Patients without prior exposure to MeCCNU or Mitomycin-C will be randomized to receive Treatment I or Treatment II.

SWOG 7634 - Stutz

PROGRESS

(77 09 - 80 09) No new patients entered during FY 80. Four patients were entered on study with no objective response. Three patients have expired and one patient is alive with disease.

The study is now closed.

STATUS: (C)

TITLE: SWOG 7635, Combined Modality Treatment of Limited Squamous Carcinoma of the Lung. Phase III.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/82

TECHNICAL OBJECTIVE

1. To determine whether chemotherapy with adriamycin and/or immunotherapy with levamisole improve median survival of split-course radiotherapy used alone in the treatment of patients with limited extent squamous bronchogenic carcinoma.
2. To determine the qualitative and quantitative toxicity of each treatment regimen.

METHOD

Patients with a histologically confirmed diagnosis of limited squamous carcinoma of the lung with no previous chemotherapy or radiation therapy will be randomized to one of the following regimens:

- Regimen A: Radiation therapy plus levamisole.
- Regimen B: Radiation therapy plus adriamycin.
- Regimen C: Radiation therapy plus adriamycin and levamisole.
- Regimen D: Radiation therapy alone.

PROGRESS

(77 10 - 80 09) No patients entered on this protocol during FY 80. In the previous year, one patient was registered, but was never treated because he was found, on tomograms, to have metastatic disease after registration, but before the start of treatment.

STATUS: (C)

TITLE: SWOG 7639, Two Adriamycin, Mitomycin C and 5-Fluorouracil Combinations in the Management of Gastric Adenocarcinoma. A Phase III Study

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/66

TECHNICAL OBJECTIVE

1. To determine and to document both the response rates and the toxicities of two different combinations of adriamycin, mitomycin C and 5-fluorouracil in the management of surgically incurable adenocarcinoma of the stomach.
2. To compare the effectiveness of these two regimens.

METHOD

Patients who have unresectable gastric adenocarcinoma and an objectively measurable lesion with no prior exposure to adriamycin, daunomycin, mitomycin C, or porfiromycin, and who meet other criteria as outlined in the protocol will be randomized to one of the two treatments.

Treatment 1: sequential regimen

adriamycin, 50 mg/M² day 1
mitomycin C, 10 mg/M² day 3
5-fluorouracil, 600 mg/M² day 29

Treatment 2: simultaneous regimen

adriamycin, 30 mg/M² per dose, day 1 and 19
mitomycin, 10 mg/M² day 1
5-fluorouracil, 600 mg/M² per dose, day 1,8,29, 36

Although one single course of therapy (8 weeks on study) would be considered as an adequate trial, an attempt should be made to administer at least two courses of therapy where possible. Patients whose disease has remained stable or has regressed on therapy will be continued on this combination for a total of two years unless the adriamycin dose limitation or drug toxicity precludes such continuation of therapy.

SWOG 7639 - Stutz

PROGRESS

(77 09 - 80 09) No new patients entered the protocol during FY 80. One patient was entered on the protocol with progressive disease and death four months later.

The study is now closed.

STATUS: (C)

TITLE: SWOG 7703, Radiation Therapy in Combination with BCNU, Dimethyl Triazeno Imidazole Carboxamide (DTIC) or Procarbazine in Patients with Malignant Gliomas of the Brain. Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 77/74

TECHNICAL OBJECTIVE

To compare the effectiveness of radiation therapy plus BCNU, radiation therapy plus DTIC, and radiation therapy plus procarbazine for remission induction, duration of remission, and survival in patients with malignant gliomas of the brain.

METHOD

Patients with histologically confirmed primary central nervous tumors of the following histologic types will be entered on the study: astrocytoma, grades 3 and 4 (glioblastoma multiforme). Other criteria: surgery with histologic diagnosis within the prior four weeks and no prior chemotherapy of any type with the exception of corticosteroids. Patients will be randomly allocated to one of the three programs: (1) radiation therapy plus BCNU; (2) radiation therapy plus procarbazine; (3) radiation therapy plus DTIC (dosage as outlined in the protocol). Since survival time is an important end point of this study, each investigator will be required to follow each patient until death and to report the death.

PROGRESS

(77 09 - 80 09) No patients have been entered on this protocol.

STATUS: (0)

TITLE: SWOG 7706, Combination Chemotherapy for Stages III and IV Ovarian Carcinoma Resistant to Adriamycin-Cyclophosphamide Treatment of Single Alkylating Agent Treatment

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/08

TECHNICAL OBJECTIVE

1. To use a combination of 5-FU, hexamethylmelamine, and platinum in an attempt to induce complete and partial clinical remissions in patients with stages III and IV ovarian carcinoma which have failed to respond to or have relapsed following remission from adriamycin-cyclophosphamide therapy.
2. To use a combination of 5-FU, hexamethylmelamine, platinum, and adriamycin to induce complete and/or partial remissions in patients with stages III and IV ovarian carcinoma who have failed on or relapsed from previous alkylating agent therapy.

METHOD

Patient Eligibility: (1) diagnosis of ovarian carcinoma established by biopsy; epithelial type neoplasms to be included; (2) only patients with pathologic stages III or IV ovarian carcinoma are eligible; patients who have relapsed after initial radiation therapy will not be eligible; (3) only patients who had previously received and had failed or relapsed following adri-CTX therapy or those having previous single alkylating agent chemotherapy will be eligible; (4) patients with a history of serious cardiac arrhythmias, myocardial infarction, or congestive heart failure will be ineligible to receive adriamycin and should be placed on the three drug regimen (cis-platinum, hexamethylmelamine, 5-FU); (5) patients with serum creatinines >1.5 mg%, BUN's >25 mg%, and creatinine clearances of <60 mg/min or obstruction to the ureters seen on IVP are ineligible for cis-platinum and should be placed on adriamycin, 5-FU, and hexamethylmelamine where appropriate, (6) measurable residual tumor is required for entry; (7) WBC must be $>2,500$ and platelets $>100,000/\text{mm}^3$. BUN should be 25 mg%, and serum creatinine <1.5 mg%. Creatinine clearance of <60 and no obstruction to the ureters by IVP.

SWOG 7706 - Stutz

Initial drug doses will be based on bone marrow reserve.

Treatment 1: Patients who have failed to respond to or relapsed from prior adriamycin-CTX.

5-fluorouracil	400 mg/M ²	IV on days 1 & 8
hexamethylmelamine	150 mg/M ²	PO daily days 1-14
plus pyridoxine	50 mg qd	days 1-14
cis-platinum	50 mg/M ²	IV infusion (1 mg/min) day 1

Treatment 2: Patients who have previously failed on or have relapsed following therapy with single alkylating agent therapy.

adriamycin	25 mg/M ²	IV on day 1
5-fluorouracil	300 mg/M ²	IV days 1 & 8
hexamethylmelamine	150 mg/M ²	PO days 1-14
plus pyridoxine	50 mg qd,	days 1-14
cis-platinum	50 mg/M ² ,	(1 mg/min) day 1

PROGRESS

(78 02 - 80 09) Two patients entered on protocol:

- (1) Partial response for 7 months; expired 12-78.
- (2) Good response for 7+ months - alive with progressive disease as of 1 Oct 80.

This study is closed.

STATUS: (C)

TITLE: SWOG 7707, Chemotherapy of Previously Treated Lymphoma Patients Using VBAP

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/15

TECHNICAL OBJECTIVE

To evaluate the frequency and completeness of response to VBAP chemotherapy (vincristine, BCNU, adriamycin, prednisone) in patients with malignant lymphoma (non-Hodgkin's disease and Hodgkin's disease) who have received prior therapy and are not eligible for higher priority studies.

METHOD

Patient Eligibility: Patients who have Hodgkin's disease or non-Hodgkin's lymphoma with measurable tumor and who have become refractory to prior treatment and are ineligible for higher priority. Patients should not have received prior myelosuppressive therapy for at least three weeks prior to this study. Prior nitrosourea or adriamycin therapy does not exclude patients so long as the cumulative dose of adriamycin does not exceed 390 mg/M². If prior therapy with vincristine resulted in permanent neurotoxicity, this agent will be deleted. Patients with history of myocardial disease are ineligible.

Treatment: These courses will be given in 21-day intervals if the blood counts are no lower than at onset of treatment:

VBAP	DAY:	1	2	3	4
Vincristine (total dose)	IV	1 mg			
BCNU mg/M ²	IV		30		
Adriamycin mg/M ²			30		
Prednisone mg/M ² , PO		60	60	60	60

The program will be continued so long as there is stable or improving disease. Adequate trial is two courses. Should remission be achieved then the medications will continue to maximum adriamycin tolerance (450 mg/M²).

SWOG 7707 - Stutz

PROGRESS

(78 05 - 80 09) No patients were entered on the protocol during FY 80. One patient was previously entered for 5 months with partial response and one patient was entered with partial response for two months and later expired.

This study is closed.

STATUS: (C)

TITLE: SWOG 7713/14, Chemoimmunotherapy in Non-Hodgkin's Lymphoma CHOP vs CHOP + Levamisole vs CHOP + Levamisole + BCG for Remission Induction Therapy: Levamisole vs No Maintenance after Remission Induction

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/02

TECHNICAL OBJECTIVE

1. To compare the effectiveness, in terms of rate of response of two chemoimmunotherapy regimens (CHOP + levamisole vs CHOP + levamisole + BCG) against CHOP for remission induction in previously untreated patients with non-Hodgkin's lymphoma.
2. For patients proven to be in complete remission after induction, to compare the duration of documented complete response obtained by continued maintenance immunotherapy with levamisole vs no maintenance therapy.
3. For patients with impaired cardiac function (not eligible for treatment with adriamycin), with mycosis fungoides, or with only a partial response to 11 courses of treatment with CHOP-levamisole + BCG, to estimate the complete response rate obtained by continued chemoimmunotherapy with COP + levamisole.
4. To estimate the CNS relapse rate in patients with diffuse lymphomas when CNS prophylaxis with intrathecal cytosine arabinoside is used.
5. To continue to evaluate the impact of systematic restaging of patients judged to be in complete remission and the value of expert hematopathology review of diagnostic material from all cases.
6. To establish baseline and serial data on immunologic status in both chemoimmunotherapy groups.

METHOD

Patients with a diagnosis of non-Hodgkin's lymphoma established by biopsy with no prior chemotherapy are eligible. Patients with chronic lymphocytic leukemia are ineligible. Patients with preexisting cardiac disease or mycosis fungoides are ineligible for the CHOP programs, but will be treated with COP + levamisole. Patients will be stratified according to nodular or diffuse histologies, adequate or impaired bone marrow reserves, presence or absence of bone marrow involvement, and performance status. Initial drug doses are based on bone marrow reserve. Treatment plans as outlined in the protocol.

SWOG 7713/14 - Stutz

PROGRESS

(77 12 - 80 09) Three patients have been registered on the protocol.

- (1) Mixed response for 6 weeks - patient later expired with CNS disease.
- (2) Complete response for one year; no evidence of disease at present.
- (3) Progressive disease on study; alive on alternative therapy.

STATUS: (0)

TITLE: SWOG 7725, Continuous 5-Drug Induction with Intermittent CMPP vs CMPP + Levamisole for Maintenance in Patients with Estrogen Receptor Negative Breast Cancer, Phase III.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/16

TECHNICAL OBJECTIVE

To determine the respective effects of levamisole on the duration of response and survival of patients with advanced breast cancer concurrently treated with maintenance chemotherapy after a successful remission induction trial of continuous Cooper regimen; and to accumulate data on immunologic variables under the conditions of chemotherapy alone and combined chemotherapy and immunotherapy with levamisole of advanced breast cancer.

METHOD

Patient Eligibility: only patients proven to be estrogen receptor negative are eligible. Patients must have a life expectancy of 2 months and measurable lesions and no previous chemotherapy other than adjuvant chemotherapy. Patients coming off additive hormonal therapy and antiestrogens must have been off therapy for 6 weeks and have increasing disease. If the 6 week observation period off hormones appears to be excessively risky, the patient may be entered provided that 3 weeks have elapsed since last day of hormonal therapy and disease is rapidly progressive. Prior surgical ablative endocrine therapy must have taken place 3 weeks prior to entry if the disease is rapidly progressive and 10 weeks if slowly progressive. Patients with previous cancer immunotherapy or who had relapsed while receiving multiple durg adjuvant chemotherapy are ineligible. Concomitant therapy with mithramycin is not allowed, and concomitant therapy with corticosteroids (other than prednisone) is allowed only in adrenalectomized or hypophysectomized patients.

Treatment: All patients will undergo a remission induction trial with continuous Cooper regimen in the following fashion:

SWOG 7725 - Stutz

Vincristine	0.625 mg/M ²	IV	once a week for 8 weeks
5-Fluorouracil	300 mg/M ²	IV	" " "
Methotrexate	15 mg/M ²	IV	" " "
Cyclophosphamide	60 mg/M ²	PO	daily for 8 weeks
Prednisone	30 mg/M ²	PO	daily for 2 weeks, reduce
	to 20 mg/M ²	PO	for next 2 weeks, reduce
	to 10 mg/M ²	until day 49, then taper to	
			nothing by day 56

Patients with increasing disease after 6 weekly induction cycles will go off study. After achievement of remission or stable status, the patients will be randomly allocated to the following treatment arms:

Army I - Maintenance "Intermittent Cooper Regimen"

5-Fluorouracil	180 mg/M ²	PO	daily x 5 days, q 28 days
Methotrexate	4 mg/M ²	PO	" " "
Cyclophosphamide	120 mg/M ²	PO	" " "
Prednisone	40 mg/M ²	PO	" " "

Arm II - Intermittent Cooper + levamisole

The same as Arm I plus levamisole 100 mg/M² daily in 3 divided doses on days 4-6, 11-13, and 18-20 of each cycle.

As with all studies, dose modifications will be made when necessary.

PROGRESS

(78 02 - 80 09) Seven patients were registered.

- (1) Progression on treatment - later expired.
- (2) Partial response for two months.
- (3) Induction phase - partial response for three weeks.
Maintenance phase - progression of disease - later expired.
- (4) Progression on treatment - later expired.
- (5) Complete response for three weeks; then progression of disease; patient alive on other therapy.
- (6) Good partial response for one year - then progression, but patient is still alive.
- (7) Complete response for 6½ months - patient alive with disease.

STATUS: (0)

TITLE: SWOG 7727/28, Combination Chemoimmunotherapy Utilizing BCNU, Hydroxyurea, and DTIC (BHD) with Levamisole versus DTIC Plus Actinomycin-D in the Treatment of Patients with Disseminated Malignant Melanoma, Phase III.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/12

TECHNICAL OBJECTIVE

To determine remission induction rates, remission duration, survival, and toxicity in patients with disseminated malignant melanoma treated with BHD (BCNU, hydroxyurea, DTIC), BHD plus levamisole, and intermittent single high dose DTIC plus actinomycin D in a prospective, randomized clinical study.

METHOD

Patient Eligibility: histologically proven disseminated malignant melanoma with no previous treatment with any of the agents involved; measurable disease and estimated survival of at least two months; adequate renal and hepatic function; BUN >25 mg% or creatinine >1.5 mg% and bilirubin >2.5 mg%; hepatic or renal metastases are eligible provided organ function is adequate; recovery from the toxic effects of prior therapy and completion of RT to bone marrow bearing areas at least two weeks prior to entry.

Brain metastasis treatment: decadron 8-12 mg/day x 3 PO then tapered at the discretion of the investigator; day 3 begin total irradiation, 4000 rads over 2 week period; chemotherapy or chemoimmunotherapy will begin on the second week of radiotherapy.

Hepatic metastasis treatment: hepatic artery cannulation via femoral artery or brachial artery route. DTIC 200 mg/M²/day over 24 hr infusion in 1000 ml of D₅W x 5 days; after 5-7 days patient will begin either chemotherapy or chemoimmunotherapy.

Patients will be stratified according to performance status and age. Treatment arms: I. (a) BHD - normal marrow (b) impaired marrow; II. (a) BHD + levamisole - normal marrow (b) impaired marrow; and III. (a) actinomycin D + high dose DTIC - normal marrow (b) impaired marrow.

If patients on BHD + levamisole or actinomycin D + DTIC have no response in the 2 initial courses, they will be crossed over. Patients not responding to BHD alone will be taken off study after an adequate trial. Dosages, courses of treatment, and

SWOG 7727/28 - Stutz

Patients not responding to BHD alone will be taken off study after an adequate trial. Dosages, courses of treatment, and modifications are given in detail in the protocol.

PROGRESS

(78 02 - 80 09) Three patients were registered. Two had severe progressive disease and one had a partial response but then relapsed. All three patients have expired due to progressive disease.

STATUS: (0)

TITLE: SWOG 7731, Anguidine in Adults with Advanced Soft Tissue and Bony Sarcomas

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/13

TECHNICAL OBJECTIVE

To determine the level of efficacy of the drug anguidine as a single agent in the treatment of advanced soft tissue and bony sarcomas in patients who have failed to respond or have relapsed on other therapeutic regimens.

METHOD

Patient Eligibility: diagnosis of soft tissue or bony sarcoma confirmed by pathologic examination of tissue; must demonstrate either primary or recurrent disease which is not amenable to control with surgery, radiotherapy, or higher priority chemotherapy; patients with prior surgery, radiation or chemotherapy are eligible if they have received no prior therapy with anguidine; patient must have measurable disease which can be followed for evidence of response; pretreatment WBC >3000/mcl; granulocytes >2000/mcl; platelets >100,000/mcl; normal hepatic function and normal renal function; patient must have been off prior chemotherapy or radiation long enough to recover from adverse effects (minimum 3 weeks); life expectancy of at least 6 weeks and performance status of at least 50% of the Karnofsky scale.

Treatment plan: all patients will receive: anguidine 4.5 mg/M² IV over 4 hr daily for 5 days. These courses will be repeated every 3 weeks as long as disease does not progress and adverse effects permit continuation.

PROGRESS

(73 02 - 30 09) No patients have been entered on this study.

STATUS: (T)

TITLE: SWOG 7732, The Effect of CMF With and Without Tamoxifen in Patients with Estrogen Receptor Positive Breast Cancer, Phase III.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/29

TECHNICAL OBJECTIVE

To determine if the antiestrogen, tamoxifen, in combination with Cytoxan, methotrexate, and 5-FU will alter the response rate, duration of response, and median survival seen with Cytoxan, methotrexate, and 5-FU alone in advanced human breast cancer in patients who are estrogen receptor positive.

METHOD

Patient Eligibility: histological proof of progressing recurrent breast cancer, measurable disease, and estimated survival greater than 10 weeks. On assay of primary or recurrent tumor, estrogen receptor must be present. WBC must be ≥ 4000 , platelet $\geq 100,000$, hematocrit ≥ 30 ; patients having abnormal creatinine and BUN > 30 or creatinine clearance < 60 are ineligible. Patients with abnormal liver function tests must have liver scan or biopsy to diagnose liver metastasis if not previously established. Prior hormonal therapy will be allowed if it was completed 4 weeks prior to entry and there is evidence of clearly progressive disease. Glucocorticoids will be allowed as replacement therapy only after adrenalectomy. Patients with prior Cytoxan, methotrexate, or 5-FU therapy; endocrine ablation less than 4 weeks prior to entry; or radiotherapy to measurable lesion within 6 weeks of entry are ineligible. Previously radiated bone lesions may not be used as the pilot lesion.

Treatment: Patients will be randomized between CMF + tamoxifen and CMF alone as shown below:

Arm I - CMF + Tamoxifen

Tamoxifen, 10mg, BID PO daily; Cytoxan 65 mg/M^2 PO daily; methotrexate 15 mg/M^2 IV weekly; 5-FU 300 mg/M^2 IV weekly.

Arm II - CMF alone - the same treatment plan as Arm I without Tamoxifen.

PROGRESS

(78 03 - 80 09) No patients were entered on protocol.

STATUS: (T)

192

TITLE: SWOG 7736, Evaluation of Anguidine in the Treatment of Urological Malignancies, Phase II.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/31

TECHNICAL OBJECTIVE

To determine the efficacy of anguidine in treating the major urological malignancies in terms of response rate, duration of response, and survival; to more fully study the adverse effects of anguidine and factors important in producing such effects.

METHOD

Patient Eligibility: patients with histologically proven advanced urological malignancies not eligible for treatment with drugs of proven or likely higher efficacy with a life expectancy of at least 6 weeks. Measurable lesions are mandatory. $WBC >4,000/\text{mm}^3$, platelet count $>100,000/\text{mm}^3$, serum bilirubin <6.0 , BUN $<40 \text{ mg/ml}$, and serum creatinine $<2.0 \text{ mg/dl}$. No radiotherapy or chemotherapy during preceding 21 days (42 days if nitrosourea) and recovered from acute toxicities of such treatment. Previous hormonal therapy in renal cell cancer is allowed, but should be stopped before entry.

Treatment: Patients will be divided into poor risk and good risk categories as defined in protocol. Anguidine must be dissolved with 500 ml of D5W and administered as an IV infusion over a period of 4 hours. The initial dose level will be as follows: Good risk: $4.5 \text{ mg/M}^2 \times 5 \text{ days}$

Poor Risk: $3.0 \text{ mg/M}^2 \times 5 \text{ days}$

Subsequent courses of treatment will be administered for 5 days at intervals of 28 days as tolerated, if the nadirs have been passed and the granulocyte count is >2000 and platelets $>100,000$. Dose modification will be made as required. An adequate trial of therapy will consist of one cycle of chemotherapy with evidence of increasing disease in the face of toxicity. Patients with improving disease or stable disease will continue treatment indefinitely with the proper dose adjustment.

PROGRESS

(78 03 - 80 09) No patients were entered on protocol.

STATUS: (T)

SWOG 7765 - Adriamycin and Single Dose DTIC in Soft Tissue and Bone Sarcomas, Phase II

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: Suresh B. Katakkar, M.D., DAC
LTC Irwin Dabe, MC

WORK UNIT NO: 80/21

TECHNICAL OBJECTIVE

To determine the effectiveness and tolerance of adriamycin and single dose DTIC in patients with metastatic sarcomas who have failed on higher priority treatment protocols.

METHOD

Patients who have failed on higher priority treatment and who have not previously received adriamycin and DTIC and who have adequate bone marrow reserve will have 60 mg/M² administered IV at 21 day intervals followed by 750 mg/M² DTIC infused over a 45 minutes period. Inadequate bone marrow reserve patients: the same procedure with adriamycin administered at a dose of 40 mg/M² and DTIC at a dose of 500 mg/M².

PROGRESS

(80 06 - 80 09) No patients have been registered on the protocol.

STATUS: (0)

SWOG 7802 - Adjuvant Therapy of Soft Tissue Sarcoma with
Radiation Therapy + Combination Chemotherapy

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: Suresh B. Katakkar, M.D., DAC
LTC H. Irving Pierce, MC

WORK UNIT NO: 79/90

TECHNICAL OBJECTIVES

To determine (1) whether combination chemotherapy with A-DIC can improve the results in terms of disease-free survival produced by adjuvant radiotherapy in patients with soft tissue sarcomas Stage IIB and III at high risk for recurrent disease; (2) any difference in toxicity between patients receiving boost radiation therapy to the scar with Cobalt 60 or electron beam; and (3) any difference in local recurrence rate or disease-free survival between patients with adequate surgery and those without.

METHOD

Patients will be stratified according to: histologic diagnosis (rhabdomyosarcoma or other); primary tumor site (abdomen or other; stage; age (<65 or >65); and adequacy of resection.

Treatment 1: radiation therapy

Treatment 2: radiation therapy plus chemotherapy (adria + DIC)

Patients with primary tumors in the abdomen, a diagnosis of rhabdomyosarcoma, and those with Stage III C or IV A will receive only radiotherapy plus chemotherapy

PROGRESS

(79 10 - 80 09) No patients were registered on the protocol. The study is now closed.

STATUS: (T)

TITLE: SWOG 7804, Adjuvant Chemotherapy with 5-Fluorouracil, Adriamycin, and Mitomycin-C (FAM) vs Surgery Alone for Patients with Locally Advanced Gastric Adenocarcinoma

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/42

TECHNICAL OBJECTIVE

To determine the efficacy of adjuvant chemotherapy with FAM on the disease-free interval and survival of patients with TNM stage-groups IB, IC, II and III gastric adenocarcinoma compared to potentially curative surgery alone.

METHOD

Patient Eligibility: patients must have TNM stage-group IB, IC, II or III gastric adenocarcinoma and no microscopic or gross residual postoperatively; no prior chemo- or radiotherapy; no medical contraindications to chemotherapy with FAM; serum bilirubin <2.0 mg/100 ml; SGOT and SGPT less than three times the upper limit of normal values; creatinine clearance >75 cc/min; BUN ≤25 mg%; serum creatinine ≤1.5 mg%; WBC >4,000; and platelets >100,000.

Treatment: After surgery, patients will be randomized to either Treatment 1 (no further therapy) or Treatment 2:
FAM - 5-FU, 600 mg/M² IV days 1 & 8, 29 & 36
adriamycin, 30 mg/M² IV days 1 & 29
mitomycin-C, 10 mg/M² IV day 1

A total of 6 courses, one every 8 weeks, will be administered. After 12 months, the active therapy phase is completed. The patient will be followed at six month intervals for five years if remission continues.

PROGRESS

(78-07 - 80-09) No patients entered on this study.

STATUS: (0)

TITLE: SWOG 7806, Cis-Diamminodichloroplatinum (II) in the Treatment of Refractory Epidermoid Carcinoma of the Esophagus, Phase II.

PRINCIPAL INVESTIGATOR LTC Friedrich H. Stutz, MC

WORK UNIT NO 78-35

TECHNICAL OBJECTIVE

To determine the response rate and survival, with some degree of precision, utilizing cis-diamminodichloroplatinum II (CACP) in the treatment of patients with squamous cell carcinoma of the esophagus which is growing despite more standard therapy.

METHOD

Patient Eligibility. Patient must have biopsy confirmed diagnosis of epidermoid carcinoma of the esophagus. Adeno-carcinoma of the esophagus is not eligible. Patient must have an absolute granulocyte count of >2,000 and a platelet count of >150,000 and must be past the present nadir resulting from any prior therapy. Patient must have a BUN of no higher than 20 mg% and a serum creatinine no higher than 1.4 mg% or creatinine clearance in excess of 75 cc/minute. Two functioning kidneys and an unobstructed urinary tract are required.

Treatment: CACP 50 mg/M² IV infusion over an 1-4 hour interval, days 1 & 8 of each 28 day course. Prior to every dose, the patient must receive at least 1,000 cc of fluids above usual intake (also on the evening before administration).

As long as there is evidence of tumor regression or disease stability at an acceptable level without unacceptable toxicity the CACP will be continued indefinitely. Although 30 days on therapy will constitute an adequate trial, an attempt will be made to give each patient two complete courses if the clinical status is acceptable.

PROGRESS

78-09 - 80-09) No patients entered on the study

STATUS: (0)

TITLE: SWOG 7807, CACP in Refractory Epidermoid Carcinoma of the Lung

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/36

TECHNICAL OBJECTIVE

To determine the response rate and survival in patients with epidermoid carcinoma of the lung who have demonstrated refractoriness to previous therapy, utilizing cis-diamminodichloroplatinum (II) (CACP).

METHOD

Patient Eligibility: Patients must have confirmed, preferably by biopsy, epidermoid carcinoma of the lung; an absolute granulocyte count of at least 2,000, a platelet count of at least 150,000, and must be past the nadir resulting from any prior therapy; a BUN >20 mg%, serum creatinine >1.4 mg% (if these two criteria are not met, a patient will be considered eligible if the creatinine clearance proves to be in excess of 75 cc/min); no evidence of obstruction of the urinary tract as determined by radiographic studies; and measurable disease.

Treatment: On the evening before and prior to drug administration, the patient will receive at least 1000 cc of fluids above usual intake (either IV or oral). The initial course will be given at a dose of 50 mg/M² IV infusion with the drug diluted in 1 liter D5½NS. This will be given on days 1 & 8, over an interval of 1-4 hours. The course will be repeated at four week intervals if BUN and serum creatinine and blood counts are at defined levels. For subsequent courses the drug dose will be modified based on the effects of the immediate previous course. CACP therapy will be continued indefinitely as long as there is evidence of tumor regression or disease stability at an acceptable level. Although 30 days on study will constitute an adequate trial, an attempt will be made, if clinically tenable, to maintain a patient on study for two complete courses.

PROGRESS

(78 09 - 80 09) Three patients were registered on this protocol.

SWOG 7807 - Stutz

- (1) Progression on treatment (2 months); expired 3 months later.
- (2) Stable disease after 3 months treatment; alive at 6 months.
- (3) Progression on treatment - patient expired.

STATUS: (C)

TITLE: SWOG 7808, Combination Modality Treatment for Stages III and IV Hodgkin's Disease, MOPP #6

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 78/47

TECHNICAL OBJECTIVE

To attempt to increase the complete remission rate induced with MOP-BAP (nitrogen mustard, vincristine, procarbazine, prednisone, adriamycin, and bleomycin) alone utilizing involved field radiotherapy in patients with Stages III and IV Hodgkin's disease achieving partial remission at the end of 6 cycles.

To determine if immunotherapy maintenance with levamisole or consolidation with low dose involved field radiotherapy will produce significantly longer remission durations over a no further treatment group when complete remission has been induced with 6 cycles of MOP-BAP in Stages III & IV Hodgkin's.

METHOD

Patient Eligibility: Patients must have histologic diagnosis of Hodgkin's disease classified by the Lukes and Butler System; no prior chemotherapy; 15 years of age or older. Patients with a history of congestive heart failure, valvular heart disease, or serious obstructive or restrictive pulmonary disease will be excluded.

Treatment: All patients except those with prior radiotherapy must receive radiation therapy consultation before chemotherapy is started.

Treatment 1: Normal marrow patients will receive 6 cycles of MOP-BAP

Treatment 2: Impaired bone marrow patients will receive 6 cycles of MOP-BAP with dose modifications.

Complete remission (CR) patients will be randomized between Treatment 3 (no treatment) and Treatment 4 (levamisole).

Treatment 3 (no treatment) and Treatment 4 (levamisole).
Partial remission (PR) patients without prior radiation therapy or residual bone marrow involvement will receive Treatment 6 (radiation therapy). PR patients with prior radiation therapy or those with residual bone marrow involvement will receive treatment 7 (4 additional cycles of MOP-BAP, after 10 total cycles of MOP-BAP, patient will continue study on MOP-BAP therapy at the discretion of the investigator). CR patients without prior radiation therapy will receive Treatment 5 (radiation therapy for CR). Doses for chemotherapy and radiotherapy can be found in para 5.0 of the protocol

SWOG 78 08 - Stutz

PROGRESS

(78 09 - 79 09) One patient was treated for 7+ months with excellent partial response. He was taken off the protocol because he chose to continue chemotherapy rather than go to radiotherapy as required by the protocol.

(79 09 - 80 09) Two patients were treated:

- (1) Complete response at 7 months
- (2) Complete response at 5 months

STATUS: (0)

TITLE: SWOG 7811 - Brain Metastases Protocol, Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 79/03

TECHNICAL OBJECTIVE

To determine the effectiveness of combined radiation therapy and metronidazole (Flagyl) in the treatment of patients with brain metastases from primary malignancies outside the central nervous system, compared with radiation therapy alone, as determined by objective response (brain and/or CAT scan) and/or increase in functional neurologic level and duration of response.

To determine the toxicity of multiple dose administration of metronidazole and radiation therapy.

METHOD

Patients will have had no prior radiation to the brain. Patients with brain metastases will be treated with whole brain irradiation therapy. A second group will be treated with whole brain irradiation therapy plus metronidazole.

PROGRESS

(79 03 - 80 09) One patient has been treated. After one course of metronidazole, patient refused further treatment because of nausea and vomiting; patient later expired.

STATUS: (0)

TITLE: Treatment of Advanced Germ Cell Neoplasms of the Testis: Remission Induction with Vinblastine, Bleomycin, with Low-Dose or High-Dose Cis-Platinum; Surgical Removal of all Residual Tumor Following Remission Induction; Maintenance Therapy with CTX, Actinomycin-D, Adriamycin and Vinblastine, Phases II-III. SWOG 7817.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 79/04

TECHNICAL OBJECTIVE

To determine in a randomized fashion the effectiveness of cis-platinum given in the conventional low-dose schedule daily x 5 days vs high-dose intermittent treatment in remission induction of disseminated testicular cancer, when combined with vinblastine and bleomycin.

To determine the survival of patients who achieve a partial remission and are rendered disease-free by surgical removal of residual disease and maintained on the same chemotherapy as patients who achieved complete remission status on chemotherapy alone.

To determine the effectiveness of cyclophosphamide, actinomycin-D, adriamycin, and vinblastine, in the maintenance of remission status.

To document the nature and extent of the hematologic and non-hematologic side effects of the various drug combinations.

METHOD

Patients with carcinoma of the testis will be treated randomly with cis-platinum utilizing the low dose schedule vs the high dose intermittent treatment when combined with vinblastine and bleomycin. These patients will then be maintained on cyclophosphamide, actinomycin-D, adriamycin, and vinblastine.

PROGRESS

(79-11 - 80-09) No patients have been entered on this protocol.

STATUS: (0)

TITLE: SWOG 7823/24/25/26 - ROAP-AdOAP in Acute Leukemia,
Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

WORK UNIT NO: 79/02

TECHNICAL OBJECTIVE

To compare the efficacy of the 4-drug combination chemotherapy regimen, ROAP (Rubidazole, Vincristine, Arabinosyl Cytosine, and Prednisone) to AdOAP (the same combination using Adriamycin in place of Rubidazole) in adult acute leukemia, as determined by remission duration and survival.

To determine the comparative toxicity of these regimens.

To determine whether late intensification therapy at 9 months after complete remission will improve long-term, disease free survival.

To determine whether immunotherapy using Levamisole for 6 months after 12 months of complete remission on chemotherapy improves disease-free survival.

To determine the effects of intrathecal Ara-C on the incidence of CNS leukemia.

To determine reproducibility of the FAB/histologic classification and correlation to response to therapy in 200 consecutive cases of acute leukemia.

To study the effects of intensive supportive care in the management of acute leukemia.

METHOD

For remission induction Group A will receive ROAP and Group B will receive AdOAP. When leukemic cells are no longer visible in the bone marrow consolidation therapy will begin with one-half the patients receiving only chemotherapy consisting of the same drugs, but in reduced dosage. The other one-half will receive the same drugs with the addition of cytosine arabinoside in the spinal fluid at weekly intervals for 8 weeks. If a complete remission persists, maintenance therapy will be given consisting of vincristine, cytosine arabinoside, and prednisone for 5 days at monthly intervals for 9 months. One half of these patients will then receive late intensification

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therapy consisting of a combination of vincristine, prednisone, and methotrexate, and 6-mercaptopurine for 5 days. The other one-half will receive 3 additional months of maintenance therapy, at which time all patients will be randomized into one group receiving no further treatment and another group receiving levamisole for 2 days of each week for 6 months.

PROGRESS

(79 04 - 80 09) Four patients have been registered on this protocol.

- (1) brief complete response - patient later died.
- (2) complete response for 7 months; then relapse and death.
- (3) complete response with one course; transferred to BAMC.
- (4) partial response with two courses; expired after CNS relapse.

STATUS: (0)

TITLE: Combined Modality Therapy for Breast Carcinoma,
Phase III - SWOG 7827

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: Suresh B. Katakkar, M.D., MC
LTC Irwin B. Dabe, MC

WORK UNIT NO: 79/96

TECHNICAL OBJECTIVES

To compare the disease-free interval and recurrence rates in: estrogen receptor positive premenopausal patients with Stage II disease using combination chemotherapy alone vs combination chemotherapy and oophorectomy;

estrogen receptor positive postmenopausal patients with Stage II disease using combination chemotherapy plus tamoxifen vs tamoxifen alone vs combination chemotherapy alone;

estrogen receptor negative patients with Stage I^T disease using one vs two years of combination chemotherapy;

To compare the effect of these various adjunctive therapy programs upon survival patterns and to correlate the estrogen receptor status with disease-free interval and survival.

METHOD

Patients with a histologically proven diagnosis of breast cancer (Stage II or Stage III) with 1 or more pathologically involved axillary nodes will receive one of the following treatments:

- (1) CMFVP for 1 yr - pre or postmenopausal ER- patients.*
- (2) CMFVP for 2 yr - pre or postmenopausal ER- patients.
- (3) CMFVP for 1 yr - premenopausal ER+ patients.
- (4) Oophorectomy + CMFVP - premenopausal ER+ patients.
- (5) Tamoxifen alone for 1 yr - postmenopausal ER+ patients.
- (6) CMFVP for 1 yr - postmenopausal ER+ patients.
- (7) Tamoxifen + CMFVP for 1 yr - postmenopausal ER+ patients.

Any patient undergoing segmental mastectomy (lumpectomy) will receive 6 wks of radiation therapy in addition to the treatment they are randomized to receive.

*C - cyclophosphamide; M - methotrexate; F - 5-fluorouracil;
V - vincristine; P - prednisone

SWOG 7827 - Stutz

PROGRESS

(80 02 - 80 09) Four patients have registered. All are doing well on treatment; too early for evaluation.

STATUS: (0)

TITLE: SWOG 7828 - Combined Modality Therapy for Extensive Small-Cell Carcinoma of the Lung.

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANT: Suresh B. Katakkar, M.D., MC

WORK UNIT NO: 79/91

TECHNICAL OBJECTIVES

To compare the efficacy of two non-cross-resistant regimens (cell-cycle specific vs cell-cycle-non-specific) during induction.

To determine whether administration of a second non-cross-resistant regimen in consolidation can convert stable disease or partial response to a better quality of response.

To determine the effect of intentional, early alternation of non-cross-resistant regimens on the complete response rate.

To determine whether reinduction at 24 and 52 weeks has a favorable effect on response duration and survival.

To determine whether administration of intrathecal methotrexate at reinduction can affect the incidence of non-brain CNS relapse.

METHOD

Patients with extensive small-cell carcinoma of the lung as confirmed by a pathologist will receive the following treatments:

INDUCTION: (6 weeks) Treatment 1: Regimen A - VMV*
Treatment 2: Regimen B - VAC*
Treatment 3: Regimen C - VMV-VAC

*VMV - Vincristine, methotrexate, VP-16

*VAC - Vincristine, adriamycin, cyclophosphamide

CONSOLIDATION: (6 weeks): Original Regimen A - CR (complete responders) receive M/VP-16;
PR (partial responders) or SD (stable disease) receive AC
Original Regimen B - CR receive AC
PR and SD receive M/VP-16
Original Regimen C - CR, PR, and SD receive M/VP-16 for 3 weeks
and AC for second three weeks

MAINTENANCE: Prophylactic WBR plus maintenance chemotherapy with Cytoxan and VP-16 for 3 courses (28 day intervals).

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At 24 weeks all patients undergo a second randomization to receive reinduction therapy or continue with maintenance chemotherapy only. All those who receive reinduction therapy will receive the original treatment plus intrathecal methotrexate. Patients randomized to receive no reinduction therapy will continue to receive cyclophosphamide and VP-16.

At 52 weeks CR's will receive no further therapy. PR's and SD's will continue to receive cyclophosphamide and VP-16 every 28 days for a total of 2 years on therapy or until progressive disease develops.

PROGRESS

(79 12 - 80 09) Two patients were registered.

- (1) complete response for 3 months followed by CNS recurrence and death.
- (2) partial response for three weeks followed by early death.

STATUS: (0)

TITLE: SWOG 7832 - Evaluation of Chlorozotocin in Lung Cancer, Phase II

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANT: Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 79/92

TECHNICAL OBJECTIVES

To determine if chlorozotocin has significant activity, as determined by response rate and median duration of response, against small cell, large cell, adenocarcinoma, or squamous carcinoma of the lung; to observe for toxicities of chlorozotocin not yet described and better define the known toxicities; and to determine factors predisposing to excessive toxicity of this agent.

METHOD

Patients are eligible for this study who have histologically proven lung cancer and who are ineligible for protocols of higher priority. If radiation therapy has been previously given to the lesion being measured, there must be clear evidence of increasing size in that lesion post radiation therapy. Patients will be divided into risk groups: poor, normal, and good. Chlorozotocin will be administered once every 6 weeks by I.V. bolus or rapid infusion (100 mg/M² for poor risk, 200 mg/M² for normal risk, and 225 mg/M² for good risk). WBC and platelets should have recovered to 4,000/mm³ and 100,000/mm³, respectively, before a new course of treatment is instituted. Patients developing overt diabetes mellitus or other significant non-hematologic toxicity relating to chlorozotocin treatment will be carefully observed and appropriate treatment administered. These patients will not be treated again unless unequivocal tumor response has been seen and toxicity has been resolved or controlled.

PROGRESS

(79 09 - 80 01) No patients were registered on this study.

STATUS: (T)

SWOG 7841 - Phase II-III Comparison of FAM + Vincristine vs
Chlorozotocin in the Treatment of Advanced Gastric
Adenocarcinoma

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: Suresh B. Katakkar, M.D., MC
LTC Irwin Dabe, MC

WORK UNIT NO: 80/22

TECHNICAL OBJECTIVES

To determine the effectiveness (as determined by response rate and survival) of 5-FU + mitomycin-C + adriamycin and vincristine (V-FAM) in the treatment of advanced, previously untreated gastric adenocarcinoma.

To determine the efficacy as determined by response rate and survival of chlorozotocin in the treatment of previously untreated gastric adenocarcinoma.

To compare the relative effectiveness of the two treatments.

To determine by crossover, after relapse or failure on V-FAM or chlorozotocin, the effectiveness as determined by response rate and survival of the alternate treatment in advanced gastric adenocarcinoma with prior therapy.

To determine the toxicities of such treatments.

METHOD

Patients with histologically proven gastric adenocarcinoma, Stage IV in extent will be randomized to the following treatments:

Treatment 1: V-FAM - one course equals 8 weeks

Treatment 2: Chlorozotocin - one course equals 6 weeks

Patients with response or stable disease should be treated again after the appropriate interval on the same treatment regimen.

Patients failing to respond or relapsing after response to their treatment arm will receive the alternative treatment.

PROGRESS

(80 06 - 80 09) No patients were registered on this protocol.

STATUS: (0)

TITLE: SWOG 7911 - Phase II Evaluation of Gallium Nitrate in Soft Tissue and Bone Sarcomas

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 79/97

TECHNICAL OBJECTIVES

To determine the efficacy of gallium nitrate in patients with soft tissue and bone sarcomas, who have failed on higher priority treatment protocols; and to determine the nature and degree of toxicity of this drug.

METHOD

Patients with histologically proven incurable advanced soft tissue and bone sarcoma with a life expectancy of at least six weeks will receive gallium nitrate as a 700 mg/M² 30 minute infusion in 200 ml normal saline every two weeks. WBC and platelets should be 4000 and 100,000 respectively before initiation of subsequent courses of treatment. Treatment will be continued as long as the patient responds. An adequate trial will be defined as two courses of therapy.

PROGRESS

(80 02 - 80 09) No patients were entered locally on this protocol. It is considered to be a completed protocol since the national group had a large enough patient entry group for statistical purposes.

STATUS: (C)

TITLE: SWOG 7912 - Gallium Nitrate in Patients with Malignant Lymphoma - Hodgkin's and Non-Hodgkin's, Phase II

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 80/02

TECHNICAL OBJECTIVE

To determine the efficacy, as measured by response rate, of gallium nitrate in patients with malignant lymphoma, both Hodgkin's and non-Hodgkin's types, in patients who have received prior therapy and are not eligible for higher priority studies; and to determine the nature and degree of toxicity of this drug.

METHOD

Patients will receive 2 liters of fluid over their normal intake within 12 hours prior to gallium nitrate administration. Just prior to administration 500 cc of normal saline will be infused over 2 hours. Patients will be treated at a dose of 700 mg/M given as a 30 min IV infusion in 200 ml of normal saline and repeated every two weeks. In the event that myelosuppression persists at day 14, bi-weekly WBC and platelet counts are to be determined and subsequent courses of gallium nitrate are to be given only when there is bone marrow recovery. Patient eligibility, response, and dosage modifications as listed in the protocol.

PROGRESS

(80 04 - 80 09) No patients were registered on this protocol.

STATUS: (0)

TITLE: SWOG 7916 - Phase II Evaluation of Gallium Nitrate
in Metastatic Urological Malignancies: Testicular,
Bladder, Prostate, and Kidney

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: MAJ Irwin Dabe, MC
Suresh E. Katakkar, M.D., DAC

WORK UNIT NO: 80/23

TECHNICAL OBJECTIVE

To determine the efficacy of gallium nitrate as determined by response and survival in patients with metastatic urological malignancies which include: testicular, bladder, prostate, and kidney; who have failed on higher priority treatment.

METHOD

Patients are eligible who are not candidates for studies of higher priority and who have histologically proven incurable advanced metastatic testicular carcinoma, bladder carcinoma, prostate or kidney carcinoma. Patients should not have had more than two previous types of combination or single agent chemotherapy trials.

All patients will be treated at a dose of 700 mg/m² given as a 30 minute IV infusion in 200 ml of normal saline. Course will be repeated every two weeks if blood counts, and liver and renal functions permit. An adequate trial will consist of two courses of therapy.

PROGRESS

(80 06 - 80 09) No patients have been registered on this protocol.

STATUS: (0)

TITLE: SWOG 7917 - Gallium Nitrate in Previously Treated Patients with Metastatic Breast Cancer, Phase II.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO. 50724

TECHNICAL OBJECTIVES

To determine the efficacy of gallium nitrate in metastatic carcinoma of the breast who have failed standard therapy; and to determine if an initially positive gallium scan predicts response.

METHOD

Patients who have histologic proof of breast cancer, currently Stage IV in extent, will be eligible. After hydration, patients will receive 700 mg/m² gallium nitrate in 250 cc normal saline over 30 minutes. Therapy will be repeated every 2 weeks if BUN, creatinine, WBC, and platelets are satisfactory. An adequate trial will consist of 7 courses of therapy (4 weeks). Patients will remain on protocol until complete remission unless unsatisfactory stable disease or increasing disease is noted after 7 courses of therapy or moderate or severe renal toxicity or clinical hearing loss occurs.

PROGRESS

080-76-80-000. No patients were registered on this protocol.

STATUS: 000

TITLE: SWOG 7918 - Evaluation of m-AMSA in Lymphoma-Hodgkin's and Non-Hodgkin's

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 79/98

TECHNICAL OBJECTIVES

To determine the antitumor activity of AMSA used in a single dose schedule in patients with Hodgkin's and non-Hodgkin's lymphoma as determined by response rate and duration of response, who have failed on higher priority treatment protocols; and to determine the nature and degree of toxicity of this drug.

METHOD

Patients with advanced Hodgkin's or non-Hodgkin's lymphoma who have failed on prior therapy, will be given m-AMSA IV in a dose of 120mg/M² for good risk patients and 90 mg/M² for poor risk patients, and adjusted doses for patients with abnormal liver function. Treatment will be given every 3-4 weeks if blood counts and liver functions permit. Two courses are considered an adequate trial.

PROGRESS

(80 02 - 80 09) No patients have been registered on this protocol.

STATUS: (0)

TITLE: SWOG 7920 - m-AMSA in Hepatocellular Carcinoma, Gallbladder Carcinoma, and Bile Duct Carcinoma, Phase II

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 79/99

TECHNICAL OBJECTIVE

To determine the efficacy of m-AMSA at a dose of 120 mg/M² IV every three weeks in producing regressions or remission in patients with hepatocellular, bile duct, and gallbladder carcinoma.

METHOD

Patients with histologically confirmed hepatocellular, gallbladder, or bile duct carcinoma beyond hope of surgical cure are eligible. Good risk patients will receive 120 mg/M² in 500 cc of Dextrose and water over one hour. Poor risk will receive 90 mg/M² and abnormal liver function patients will receive 60 mg/M². Courses will be repeated every 3-4 weeks if WBC is greater than 3500 and platelet count is greater than 100,000 and liver functions have returned to baseline. An adequate trial will be defined as two courses of therapy. Patients will remain on therapy as long as they respond.

PROGRESS

(80 02 - 80 09) Two patients were registered: (1) had progression on treatment and was taken off study after one month; and (2) had progression on treatment and was taken off study after one month, expired 4 months later.

STATUS: (0)

TITLE: SWOG 7921 - Phase II Evaluation of MGBG in Metastatic Carcinoma of the Breast

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakker, M.D., DAC

WORK UNIT NO: 79/100

TECHNICAL OBJECTIVES

To determine response rate and remission duration with weekly intravenous therapy using MGBG in patients with carcinoma of the breast who have failed on higher priority treatment protocols.

METHOD

Patients must not be eligible for SWOG studies of a higher priority and must have histologically proven incurable metastatic carcinoma of the breast. MGBG will be given in an initial dose of 600 mg/M² IV in D₅W or normal saline over no less than 30 minutes. The drug will be given on a weekly schedule providing the WBC is greater than 3000, platelet count is greater than 100,000, and the patient has recovered from any encountered stomatitis. An adequate trial will consist of 3 courses of treatment. Patients will continue on treatment as long as they respond and tolerate toxicity.

PROGRESS

(80 02 - 80 09) No patients were registered on this protocol.

STATUS: (0)

TITLE: SWOG 7923 - Gallium Nitrate in Metastatic Squamous Cell CA and/or Local Recurrence Squamous Cell CA of the Head and Neck.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh E. Katakkan, M.D., DAC

WORK UNIT NO: 80/25

TECHNICAL OBJECTIVES

To determine the efficacy as determined by response rate of gallium nitrate in patients with metastatic squamous cell carcinoma and/or local recurrent squamous cell carcinoma of the head and neck who have failed on higher priority treatment protocols; and to determine if gallium scan results may be predictive of anti-tumor effect.

METHOD

Patients who have histologically confirmed incurable, advanced metastatic squamous cell carcinoma or local recurrent squamous cell carcinoma of the head and neck are eligible. Patients after hydration will receive 700 mg/m² gallium nitrate in 250 cc normal saline over 30 minutes. This course will be repeated every 2 weeks if BUN, creatinine, WBC, and platelets are satisfactory. An adequate trial will consist of 2 course of therapy (4 weeks). Patients will be treated until either complete remission or increasing disease is noted.

PROGRESS

(80-05 - 80-09) No patients were registered on this protocol.

STATUS: (0)

TITLE: SWOG 7924 - Multimodal Therapy for Limited Small Cell Carcinoma of the Lung, Phase III.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 80/26

TECHNICAL OBJECTIVES

To determine the efficacy of sequentially alternating mutually noncross-resistant, multidrug regimens in remission induction and intensification therapy in patients with limited small cell lung carcinoma; to determine the value of chest radiotherapy added to intensive systemic chemotherapy in reducing chest recurrences and in improve of survival; to determine the relative efficacy and toxicity of low-dose, extensive chest radiation when used in close chronologic sequence with systemic multiagent chemotherapeutic regimens; to determine whether radiotherapy ports should be set according to tumor size prior to or after induction chemotherapy; and to determine the value of combined systemic chemotherapy and radiotherapy in the control of bulky chest disease.

METHOD

Patients with histologically or cytologically confirmed small cell carcinoma of the lung are eligible. Patients will be treated for 8 weeks with combination chemotherapy of methotrexate, vincristine, VP-16, adriamycin, and cyclophosphamide. Following the completion of induction chemotherapy, patients will be treated as follows: Complete remission: patients will be randomized to receive either chest and whole brain radiotherapy followed by chemotherapy or whole brain radiotherapy alone followed by chemotherapy. Partial remission or stabilized disease: patients will be randomized to receive either extended field and whole brain radiotherapy followed by chemotherapy or involved field and whole brain radiotherapy followed by chemotherapy. Patients with progressive disease after induction chemotherapy will go off study.

PROGRESS

(80 06 - 80 09) Two patients have been registered on the study. Both patients are showing good response to the induction therapy.

STATUS: (0)

TITLE: SWOG 7927/28 - Chemotherapy for Multiple Myeloma,
Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 80/27

TECHNICAL OBJECTIVES

To compare the effectiveness of four different drug combinations for remission induction in previously untreated patients with multiple myeloma; and, for patients with a 75% tumor reduction, to evaluate the role of 12 months of chemotherapy maintenance with vincristine, cyclophosphamide, and prednisone vs these drugs plus levamisole, when compared with previous experiences.

METHOD

Patients previously untreated with chemotherapy (except prednisone) with a diagnosis of multiple myeloma, Stage I, II, or III, will be eligible for the study. Patients will receive remission induction treatment with one of the following: (1) vincristine, melphalan, cyclophosphamide, and prednisone (VMCP) for 3 courses followed by vincristine, BCNU, adriamycin, and prednisone (VBAP) for 3 courses, every 3 weeks; (2) VMCP for 3 courses followed by VBAP for 3 courses every 3 weeks plus levamisole; (3) vincristine, cyclophosphamide, and prednisone (VCP) every 3 weeks; or (4) VCP every 3 weeks plus levamisole. Treatment will continue on all regimens for a minimum of 6 months, until a 75% tumor reduction has occurred, but no longer than 18 months in the absence of remission. Patients who are responsive to remission induction with Treatments 1 or 3 will receive maintenance treatment with VCP. Patients responsive to induction therapy with Treatments 2 or 4 will receive maintenance treatment with VCP plus levamisole. Treatment cycles are repeated at 21 day intervals for 12 months provided the absolute granulocyte count is at least 1,000 and the platelets count is at least 80,000.

PROGRESS

(80 06 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: SWOG 7931 - Evaluation of AMSA in Metastatic or Advanced Adenocarcinoma of the Stomach and Pancreas, Phase II.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 80/28

TECHNICAL OBJECTIVES

To determine the antitumor activity of AMSA as determined by response rate and duration of response used in a single dose schedule in patients with metastatic adenocarcinomas of the stomach and pancreas who have failed on higher priority treatment protocols; and to determine the nature and degree of toxicity of this drug.

METHOD

Patients who are ineligible for SWOG studies of higher priority who have histologically proven, incurable, advanced metastatic adenocarcinoma of the stomach or pancreas are eligible. Good risk patients will receive AMSA in a single dose schedule: 120 mg/M² dissolved in 500 ml of D/W and infused IV over no less than one hour. Poor risk patients will start at a dose of 90 mg/M². After bone marrow and liver function recovery, repeat courses of AMSA will be given at 21 day intervals. Patients will be removed from the study if increasing disease is noted after 2 courses of therapy.

PROGRESS

(80 06 - 80 09) Two patients were registered on this protocol: (1) was registered but never treated due to sudden complications, expired July 1980; (2) received one course of mAMSA in August 1980 without response, expired 16 days later of her cancer.

STATUS: (0)

TITLE: SWOG 7934 - Evaluation of AMSA in Metastatic Squamous Carcinoma of the Head and Neck

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 80/29

TECHNICAL OBJECTIVES

To determine the antitumor activity, response rate and duration of response in patients with metastatic squamous cell carcinoma of the head and neck who have failed on higher priority treatment protocols; and to determine the nature and degree of toxicity of this drug.

METHOD

Patients who are not eligible for SWOG studies of higher priority with histologically proven incurable metastatic or locally advanced squamous cell carcinoma of the head and neck are eligible for this study. Good risk patients will receive AMSA in a 3 day schedule of $40 \text{ mg/M}^2/\text{d} \times 3$ IV. AMSA will be dissolved in 500 ml of D/W and infused IV over no less than one hour. Poor risk patients will start at a dose of $30 \text{ mg/M}^3/\text{d}$. Upon adequate bone marrow and liver function recovery, repeat courses will be given at 21 day intervals. An adequate trial will be defined as 2 courses of therapy.

PROGRESS

(80 06 - 80 09) No patients were registered on this protocol.

STATUS: (0)

TITLE: SWOG 7935 - Chemotherapy of Functioning and Non-Functioning Islet Cell CA with Chlorozotocin, Phase II.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 80/30

TECHNICAL OBJECTIVES

To study the response of functioning and non-functioning islet cell carcinoma to chlorozotocin and to obtain pathology materials for review on all patients entered into this study.

METHOD

Patients who have a biopsy-proven diagnosis of islet cell carcinoma not amenable to further surgical therapy with a life expectancy of at least six weeks are eligible. Patients treated with streptozotocin will be analyzed separately. All patients will receive chlorozotocin at six week intervals - good risk at 200 mg/M² IV bolus or rapid infusion and poor risk at 100 mg/M². Subsequent courses of treatment will be repeated every six weeks assuming hematologic recovery as manifested by a WBC greater than 4000 and platelets greater than 100,000, and a normal BUN and creatinine value. An adequate trial is one course of therapy. Therapy will be continued in the presence of stable disease or in the presence of a response until increasing disease is apparent.

PROGRESS

(80 06 - 80 09) No patients were registered on this protocol.

STATUS: (0)

TITLE: SWOG 7937 - Evaluation of m-AMSA in Metastatic Carcinoma of the GU Tract Except Renal Carcinoma, Phase II.

PRINCIPAL INVESTIGATOR: LTC Freidrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 80/31

TECHNICAL OBJECTIVES

To determine the antitumor activity of m-AMSA in patients with metastatic carcinoma of the genito-urinary tract as determined by response rate, duration of response, and survival, who have failed on higher priority treatment protocols; and to determine the nature and degree of toxicity of this drug.

METHOD

Patients with histologically confirmed incurable metastatic carcinoma as follows are eligible: renal pelvis transitional cell carcinoma, bladder transitional cell carcinoma; prostatic adenocarcinoma; all other malignancies (except renal) may be entered by specific cell-type and will be evaluated separately. Good risk patients will receive AMSA in a single dose of 120 mg/m² dissolved in 500 ml of D/W infused IV over no less than one hour every 21 days. Poor risks will receive 90 mg/m². If bilirubin is greater than 2 mg%, the initial dose will be 75 mg/m². An adequate trial is defined as two courses of therapy. Subsequent courses of AMSA are to be given only when there is full bone marrow recovery. Patients will remain on the protocol as long as they respond or until they experience intolerable toxicity.

PROGRESS

(80 02 - 80 09) No patients were registered on this protocol

STATUS: (0)

TITLE: SWOG 7940/41/43 - Evaluation of 5-FU vs A Phase II Drug in Metastatic Adenocarcinoma of the Large Bowel, Phase II-III.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 80/65

TECHNICAL OBJECTIVES

To determine the relative activity of a Phase II Drug (MGBG or gallium nitrate) in previously untreated patients with disseminated colon and rectal cancer; to compare the survival of patients with disseminated colon cancer receiving MGBG or gallium nitrate as first therapy to the survival of patients receiving a fluorinated pyrimidine, 5-FU therapy first; and to determine the effect of previously administered MGBG or gallium nitrate on the response rate seen with 5-FU in patients with disseminated colon and rectal cancer.

METHOD

Patients must have biopsy proven adenocarcinoma arising from the colon or rectum to be eligible. Patients will be randomized in to Arm I (chemotherapy with 5-FU) or Arm II (chemotherapy with either MGBG or gallium nitrate). Arm I will receive 5-FU by IV bolus injection days 1-5, repeated every four weeks. Arm II will receive either MGBG every week to be given as an IV infusion in D5W or NS over no less than 30 minutes into a freely running IV or gallium nitrate given as a 30 minute IV infusion in 200 ml of normal saline, repeated every two weeks. Upon response/relapse or disease progression, patients will be crossed-over to the opposite treatment arm providing they meet eligibility criteria.

PROGRESS

(80 09 - 80 09) No patients were registered on this protocol.

STATUS: (0)

TITLE: SWOG 7958 - Evaluation of m-AMSA in Metastatic or Recurrent Epithelial Carcinomas of the Female Genital Tract, Phase II.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 80/37

TECHNICAL OBJECTIVES

To determine the antitumor activity of AMSA in patients with metastatic or recurrent epithelial carcinomas of the ovary, endometrium, cervix, vagina, or vulva who have failed on higher priority treatment protocols; and to determine the nature and degree of toxicity of AMSA in patients treated by the split-course three-day schedule.

METHOD

Patients are eligible who have a histologically proven diagnosis of incurable advanced metastatic or recurrent epithelial carcinoma of the ovary, endometrium, cervix, vagina, or vulva. The patients will be divided into two treatment groups: good risk patients and poor risk patients. All patients will be treated by a split dose, 3-day schedule. Dose for good risk: 40 mg/M²/day, IV, for three days. Dose for poor risk: 30 mg/M²/day, IV, for three days. Total daily dose will be dissolved in 250-500 ml of D/W and given IV over one hour. Repeat courses of AMSA will be given at 21 day intervals. In the event that myelosuppression persists at day 21, biweekly WBC and platelet counts will be done and subsequent courses of AMSA will be given only when there is bone marrow recovery.

PROGRESS

(80 07 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: SWOG 7959 - Evaluation of MGBG in Metastatic Renal Carcinoma

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 80/38

TECHNICAL OBJECTIVES

To determine the response-rate and remission duration with weekly intravenous therapy using MGBG in patients with metastatic renal carcinoma; and to define the qualitative and quantitative toxicity of this regimen.

METHOD

Patients with a histologically proven diagnosis of incurable, advanced metastatic renal cell carcinoma will be eligible. MGEV will be given at a dose of 600 mg/m² as an IV infusion in D5W or NS over no less than 30 minutes into a freely running IV. The drug will be given on a weekly schedule providing the WBC is greater than 3,000/mm³ and the platelet count is greater than 100,000/mm³ (or have returned to baseline if the initial values are lower than this) and the patient has recovered from any encountered stomatitis, muscle weakness or drug induced pain. An adequate trial will consist of three courses of treatment.

PROGRESS

(80 07 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: SWOG 7965 - Chemotherapy or Chemotherapy and Immunotherapy Following Initial Surgery and/or Radiotherapy for Treatment of Early Squamous Cell Cancer of the Head and Neck

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkur, M.D., DAC

WORK UNIT NO. 80/32

TECHNICAL OBJECTIVE

To determine if the disease-free interval and survival of patients in high risk categories of squamous head and neck cancer can be improved by adjuvant methotrexate after initial surgery, radiotherapy or both have resulted in no clinically evident disease.

METHOD

Patients with histologically confirmed squamous cell carcinoma of the head and neck who have been rendered clinically disease free by surgery or radiotherapy with the following stages and sites are eligible: Pharynx Stage I-IV (MO); supraglottic and glottic larynx Stage II and IV and subglottic larynx Stage I-IV (MO); oral cavity Stage II-IV (MO); and nasal cavity/paranasal sinus Stage I-IV (MO). These patients will be randomized to receive either no treatment or MTX at a dose of 12 mg/M² IV daily for 3 days every 21 days for one year or until relapse or inability to tolerate drug because of toxicity.

PROGRESS

(80-04 + 80-09) No patients were registered on this protocol.

STATUS: (0)

TITLE: SWOG 7980 - Study of Cis-Diammine Dichloroplatinum (DDP) for Recurrent Gliomas, Phase II.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., DAC

WORK UNIT NO: 80/39

TECHNICAL OBJECTIVES

To determine the efficacy of the chemotherapeutic agent DDP in the treatment of gliomas recurrent after prior therapy with irradiation (plus or minus chemotherapy); and to determine the duration of response and survival of patients receiving this therapy.

METHOD

Patients with gliomas (Grade I-IV) who have recurred following cranial irradiation will be eligible. The starting dose for all patients will be 35 mg/M²/day given IV on 3 consecutive days. The next course of chemotherapy will be initiated in 3-4 weeks as long as blood counts have recovered and the serum creatinine, BUN, and creatinine clearance measurements are satisfactory. A minimum of 2 courses of therapy will be considered an adequate trial to evaluate efficacy and toxicity. A course is defined as a treatment plus a 3 week observation period.

PROGRESS

(80 07 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: SWOG 7982 - Chlorozotocin in the Treatment of Advanced Sarcomas, Phase II.

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabe, MC
Suresh B. Katakkar, M.D., MC

WORK UNIT NO.: 80/47

TECHNICAL OBJECTIVES

To determine if chlorozotocin in a dose of 120 mg/M² has significant activity in sarcomas by determination of response rate and duration; and to describe toxicities of chlorozotocin not yet defined.

METHOD

Patients with a biopsy-proven diagnosis of soft-tissue or bone sarcoma are eligible for the study. Patients will begin treatment on chlorozotocin at 120 mg/M² IV bolus every six weeks. An adequate trial will consist of one course of treatment (6 weeks). Subsequent courses will be given in those patients achieving a tumor response or stable disease provided WBC and platelet counts are satisfactory.

PROGRESS

(80 07 - 80 09) One patient has been on the study for one month; this is not long enough to determine results.

STATUS: (0)

TITLE: SWOG 7985 - Combined Modality Treatment for ER- Breast Cancer, Phase III

PRINCIPAL INVESTIGATOR: LTC Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC
Surech B. Katakkar, M.D., DAC

WORK UNIT NO: 80/66

TECHNICAL OBJECTIVES

To compare disease-free interval and survival among control group Stage I (and Stage II node negative) breast cancer patients whose tumors are determined to be ER- at the time of mastectomy, versus Stage I (and Stage II node negative) ER- patients treated with adjuvant cyclophosphamide, methotrexate, 5-FU, and vincristine (CMF) for 6 months; and to document recurrence patterns among untreated patients with Stage I breast cancer whose tumors are determined to be ER- at the time of mastectomy.

METHOD

Patients must have undergone a radical, modified radical or total mastectomy, or segmental mastectomy with axillary node dissection for potentially curable, histologically proven breast carcinoma, whose axillary nodes are negative for tumor and whose estrogen receptor assay on the primary tumor is less than 10 fetamoles/mg cytosol protein in order to be eligible for study (Stage I or II, node negative). Patients with bilateral malignancies are ineligible. Patients will be stratified by tumor size, type of mastectomy, and menopausal status. They will be randomized to Arm I to receive no further treatment until relapse or Arm II to receive combination chemotherapy with CMF for 6 months on a 21 day cycle if WBC's and platelets are satisfactory. Patients who receive a segmental mastectomy must receive post-operative radiation therapy which satisfies the radiation therapy guidelines in this protocol. Chemotherapy must be started by 28 days post-segmental mastectomy even though the patient will still be receiving radiation therapy.

PROGRESS

(80 09 - 80 09) No patients were registered on this protocol.

STATUS: (0)

TITLE: SWOG 7909 - Interroup Testicular Study

PRINCIPAL INVESTIGATOR: LTC Friedrich B. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin Dabé, MC
Suresh B. Katakam, M.D., DAC

WORK UNIT NO: 80133

TECHNICAL OBJECTIVES

(1) To compare the disease-free survival and overall survival for surgery alone (with chemotherapy for relapsers) vs surgery plus early adjuvant chemotherapy in patients with resectable Stage II testicular cancer. (2) To register and follow patients with non-seminoma, non-choriocarcinoma Stage I testicular cancer to define prognostic variables which may predict recurrence in this stage group. (3) To define the difference in disease-free rates and patterns of recurrence, based upon histologic subtypes and extent of disease on initial presentation. (4) To evaluate the role of marker substances such as BCG, alpha-fetoprotein, and lactate dehydrogenase in the early detection and management of recurrence in patients with Stage I and Stage II testicular carcinoma. (5) To evaluate the accuracy of lymphangiograms, CAT scans, and ultrasound studies for staging of retroperitoneal nodal involvement.

METHOD

Patients with histologically confirmed carcinoma (not pure seminoma or choriocarcinoma) of the testis Stage I (limited to testis and adjacent structures) or Stage II (extends beyond the testis but not beyond the regional draining lymph node region) who have had an orchiectomy will be eligible. Patients will undergo bipedal lymphangiogram with the intent of retroperitoneal node dissection. Serum markers may be obtained and studied prior to orchiectomy and must be obtained prior to lymphadenectomy and one and two weeks after. If at two weeks any marker is positive but falling, markers should be repeated at 3-4 weeks and the 4-week value must be normal or serial determinations must be declining with time at a rate predicted by the known serum half-life of the marker. Entry will be at 2-4 weeks post-operatively. Stage I patients will be followed routinely and tumor markers should be negative 4 weeks postop. Stage II unresectable patients are not eligible. Stage II resectable patients will be treated

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in two treatment groups. Group I: no adjuvant chemotherapy with monthly followup until recurrence. Group II: adjuvant chemotherapy with vinblastine, bleomycin, and cis-platinum. Stages I and II who were originally randomized to the follow-up group and Stage II relapsing after chemotherapy will be further treated with vinblastine, bleomycin, and cis-platinum. Patients in complete or partial remission or showing improvement after relapse induction will receive maintenance treatment with vinblastine, repeated every 4 weeks until complete remissions have received 104 weeks of therapy and partial remissions and improvements may continue indefinitely. All other patients will go off study.

PROGRESS

((80 04 - 80 09) No patients were registered on this protocol.

STATUS: (0)

CHILDRENS CANCER STUDY GROUP PROTOCOLS

PRINCIPAL INVESTIGATOR

Charlene P. Holt, LTC, MC

PROFESSIONAL ASSISTANT

Alan D. Mease, MAJ, MC

TITLE UCG 051 - Evaluation of Diglycoaldehyde for Previously Treated Children with Acute Leukemia (Phase II)

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO. 79/29

TECHNICAL OBJECTIVE

To determine the therapeutic efficacy of diglycoaldehyde in acute leukemia and solid tumors of childhood.

METHOD

Patients with histologic proof of acute leukemia, with a life expectancy of at least 12 weeks, who are resistant to current standard methods of therapy are eligible for this study. Diglycoaldehyde, 1.5 gm/M²/day x 5, I.V. over 4-6 hours, will be given every 14 days. An adequate trial will consist of a minimum of two courses. Patients with complete remission at day 28 or with complete or partial remission at day 56 will receive maintenance therapy with diglycoaldehyde, 1.5 mg/M²/day x 5, IV, every 28 days.

PROGRESS

(80 06 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: CCG 053 - 4'Demethyl-Epiposophyllotoxin-B-D-Ethylidene Glucoside (VP 16-213) (NSC-141540) for the Treatment of Refractory Childhood Acute Myelomonocytic, Myelocytic, Monocytic or Histiocytic Leukemias and Refractory Hodgkin's Disease and Non-Hodgkin's Lymphomas

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/30

TECHNICAL OBJECTIVES

(1) To determine the therapeutic efficacy of VP 16-213 in refractory childhood acute myelogenous, acute monocytic and acute monomyelocytic leukemia as well as in refractory patients with lymphomas or Hodgkin's disease. (2) To determine if the specificity of response in acute myelomonocytic, monocytic, and myelocytic leukemia and non-Hodgkin's lymphomas in childhood is similar to that reported in adult patients. (3) To determine if there is any response in a variety of refractory solid tumors in childhood.

METHOD

Patients with histologic proof of acute monocytic, myelomonocytic, myelocytic, histiocytic, or erythrocytic leukemia, with a life expectancy of at least 8 weeks, who are resistant to standard therapy and who have had no prior exposure to this agent are eligible for the study. Patients will receive VP-16, 100 mg/ M^2/d x 5 on days 1-5; 100 mg/ M^2 x 5 on days 15-20; and 125 mg/ M^2/d x 5 on days 29-33. At this point those patients with no response, progressive disease, or excessive toxicity will be taken off the study. Patients with complete or partial remission or stable disease will receive maintenance therapy of VP-16 100 mg/ M^2/d x 2 (on consecutive days) every 14 days.

PROGRESS

(80-06 - 80-09) No patients have been registered on this protocol.

STATUS: (0)

TITLE: CCG 054 - 4'Demethyl-Epipodophyllotoxin- β -D-Thenylidene Glucoside (VM-26) for the Treatment of Refractory Childhood Malignancies, Phase II.

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease MC

WORK UNIT NO: 79/31

TECHNICAL OBJECTIVES

(1) To determine if weekly high-dose VM-26 is active in pediatric malignancies. (2) Specifically, to investigate the effectiveness of weekly VM-26 in primary or metastatic brain neoplasms, Hodgkin's disease, non-Hodgkin's lymphoma, neuroblastoma, Wilms' tumor and the sarcomas. (3) To determine if weekly VM-26 dosage can in certain instances be augmented above 130 mg/M^2 and to correlate clinical toxicity with renal and hepatic dysfunction.

METHOD

All children with any malignant disease refractory to conventional therapy will be eligible. Emphasis will be placed on trials in primary or metastatic brain tumors, all lymphomas, Wilms' tumor, neuroblastoma, and the sarcomas. Patients in hematologic relapse with acute leukemia are eligible but will not be encouraged. Patients with acute non-lymphocytic leukemia or the histiocytic types of lymphoma will be treated with VP-16-213 first. Patients will receive $130 \text{ mg/M}^2/\text{wk} \times 3$, then $150 \text{ mg/M}^2/\text{wk} \times 3$. Each patient will receive at least six weeks of therapy. If the disease is progressive after six weeks, VM-26 will be discontinued. On day 42 the dosage will be increased to $180 \text{ mg/M}^2/\text{wk}$ for 3 weeks. If the patient is responding at the end of this period, the same dosage will be continued. Non-responders will be taken off the study.

PROGRESS

(80 06 - 80 09) No patients have been registered on this study.

STATUS: (0)

TITLE: CCG 061 - Evaluation of Dianhydrogalactitol for the Treatment of Refractory Childhood Malignancies

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Meuse, MC

WORK UNIT NO: 79/23

TECHNICAL OBJECTIVE

To determine the therapeutic efficacy of dianhydrogalactitol in acute leukemia and solid tumors of childhood.

METHOD

All patients with acute leukemia or with histologic proof of malignant solid tumor resistant to standard methods of therapy who have had no prior exposure to dianhydrogalactitol, will be eligible for this study. An adequate trial will consist of a minimum of two courses of treatment. Dose schedule for acute leukemia is 50 mg/ M^2 /day dianhydrogalactitol x 5, IV push or fast drip every 14 days. Dose schedule for solid tumor will be 37.5 mg/ M^2 /day x 5 IV push or fast drip every 14 days. If in those with acute leukemia, M₁ is observed by day 18 or day 56 or M₂ is observed by day 56, the patient will continue on 50 mg/ M^2 /d x 5, IV every 28 days. If, in those patients with solid tumor, complete remission is observed at day 18 or day 56 or partial remission is observed at day 56, the patient will then receive 50 mg/ M^2 /day x 5, IV, every 28 days.

PROGRESS

(79-10 - 80-09) No patients have been registered on this protocol.

STATUS: (0)

TITLE: CCG 071 - Evaluation of Cis-Platinum Diamine Dichloride (CPDD) for Previously Treated Children with Solid Tumors, Phase II.

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/33

TECHNICAL OBJECTIVES

To define the toxic and therapeutic effect of CPDD at 3 mg/kg administered with aggressive hydration and diuresis for various advanced pediatric solid tumors.

METHOD

Patients with any solid tumor will be eligible. Patients will be hospitalized. All patients, except osteogenic sarcomas, will have 3 mg/kg CPDD administered every three weeks. Osteogenic sarcoma patients will have 4.5 mg/kg every three weeks. If no response is obtained after three doses, the primary physician may elect to escalate the dose to 4.5 mg/kg every three weeks or remove the patient from the study.

PROGRESS

(80 06 - 80 09) No patients have been registered on this study.

STATUS: (0)

TITLE: CCG 072 - Evaluation of Vindesine for Previously Treated Children with Acute Non-Lymphocytic Leukemia and Solid Tumors, Phase II

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/24

TECHNICAL OBJECTIVE

To determine the efficacy of Vindesine in acute non-lymphocytic and myelogenous leukemia and solid tumors of childhood in a Phase II study.

METHOD

Only patients with histologic proof of acute non-lymphocytic leukemia who are resistant to standard modalities of therapy are eligible for this study. Patients should have a life expectancy of at least 12 weeks and must have an M-3 marrow. Patients with histologic proof of malignancy who are resistant to standard modalities of therapy will be eligible for solid tumors. An adequate trial should be considered a minimum of three complete injections. Vindesine will be continued as long as there is objective or subjective response. The dosage for this study is 4 mg/ M^2 IV as a bolus every week.

PROGRESS

(79 09 - 80 09) One patient was registered on this protocol. There was minimal toxicity and a partial response for two months before relapse and death from disease.

STATUS: (0)

TITLE: CCG 075 - Evaluation of Azapicyl in the Treatment of Children with Rhabdomyosarcoma and Undifferentiated Sarcoma Resistant to Conventional Therapy, Phase II

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/34

TECHNICAL OBJECTIVE

To determine the therapeutic effect of azapicyl in rhabdomyosarcoma and undifferentiated sarcoma which have become resistant to conventional therapy.

METHOD

Only patients with rhabdomyosarcoma or undifferentiated sarcoma (recurrent or metastatic tumor unresponsive to conventional therapy) are eligible for this study. The initial drug dose will be 350 mg/M²/day in two divided doses orally. This dose will be continued for two weeks. If no response has begun to occur at two weeks, the dose will be increased to 400 mg/M²/day for two weeks. If any tumor regression is apparent at four weeks, but regression is not complete, the dose will be increased to 450 mg/M²/day for two weeks. If complete regression is present at 2, 4, or 6 weeks, the drug dose that the patient is on when complete remission occurs will be maintained until disease is recurrent or toxicity intervenes.

PROGRESS

(80 06 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: CCG 081 - Evaluation of β -Deoxythioguanosine (β -TGdR) for the Treatment of Refractory Leukemias of Children

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/25

TECHNICAL OBJECTIVE

To determine the effectiveness of β -TGdR in the acute leukemias of childhood that are resistant to standard methods of treatment.

METHOD

Patients with acute leukemia who are resistant to current standard methods of therapy including all non-investigational drugs effective in leukemia and having an M₃ marrow and who have had no prior exposure to β -TGdR will be eligible for the study. β -TGdR will be given at a dose of 1,750 mg/M²/dose every 12 hour, repeated three times, which will constitute one course. The drug will be infused with 5% dextrose solution over a four hour period. Each course will be given every two weeks unless modified by toxicity. An adequate trial shall consist of three courses of β -TGdR. Those patients with M₁ on day 14, 28, or 42 or M₂ on day 42 will receive a maintenance dose of 1,750 mg/M²/dose every 12 hours, repeated three times, every three weeks.

PROGRESS

(79 10 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: CCG 083 - Evaluation of Prednimustine in Refractory
Acute Leukemia, Phase II

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/95

TECHNICAL OBJECTIVE

To determine the therapeutic efficacy and toxicity of prednimustine in children with refractory leukemia.

METHOD

Patients with acute leukemia resistant to all conventional chemotherapy will be eligible. Patients will receive 40 mg/M²/day prednimustine in two divided oral doses. Administration will continue until the onset of progressive symptomatic disease or for a minimum of eight weeks. If a patient achieves a complete response, the dose will be halved and the drug continued as a single daily oral dose. In patients with no bone marrow disease during therapy, prednimustine will be discontinued temporarily for ANC less than 1,000 or platelet count less than 75,000. When counts improve prednimustine will be started at a dose 10 mg/M² less than the previous dose. In patients in relapse, if the white count continues to rise at two weeks, the daily dose may be escalated 20 mg/M²/day. Patients may be taken off study for progressive symptomatic disease after four weeks, recurrent disease after a response, or for intractable side effects. When the drug is discontinued, patients will be supported with a dose about one half the daily dose and weaned with every other day dosage. Patients will be evaluated each week with interval history, physical examination including BP and weight, urine glucose, and CBC.

PROGRESS

(80 03 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: CCG 161 - Treatment of Newly Diagnosed Acute Lymphoblastic Leukemia for Patients with "Low Risk" Prognostic Characteristics

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO. 79/26

TECHNICAL OBJECTIVES

(1) Modification of therapy to reduce toxicity and long-term morbidity in children with "low risk" ALL without compromising the excellent prognosis of this group; (2) evaluate by randomization the need for cranial irradiation for CNS prophylaxis by comparing the efficacy of cranial irradiation, 1800 R, plus IT methotrexate vs IT methotrexate plus maintenance IT methotrexate; (3) evaluate by randomization the efficacy and toxicity of monthly vincristine and prednisone in maintenance; (4) determine if factors other than age at diagnosis and initial WBC are important risk factors; (5) evaluate the prognostic significance of surface marker analysis of leukemic blast cells at diagnosis and relapse; (6) determine the effect of total drug dose/ M^2 /unit time on remission duration and survival; and (7) analyze patients who relapse or die in remission for features such as intercurrent illness, deviations and lapses in therapy, and cell surface markers in an attempt to better define prognostic groups and reasons for treatment failure.

METHOD

Patients 3-5 years of age at diagnosis, previously untreated for acute lymphoblastic or undifferentiated leukemia, are eligible. All patients will receive identical induction therapy consisting of vincristine, prednisone, and L-asparaginase plus IT methotrexate. Patients will be randomized on day 28 to receive IT methotrexate plus oral 6-MP with or without cranial irradiation (days 28-56). Maintenance will consist of two regimens, one receiving 6-MP plus oral methotrexate and one receiving 6-MP and oral methotrexate plus vincristine and prednisone. These will be subregimented into those who received cranial irradiation and those who did not. The groups not receiving irradiation will also receive IT methotrexate on the last day of this 7 week cycle. The 7 week cycle is to be repeated for a total of 12 cycles. At the end of the 12 cycles, all therapy will be discontinued for those patients in continuous complete remission, and they will be observed for remission duration and survival provided that chemotherapy beyond three years is not beneficial.

CCG 161 - Holt

PROGRESS

(79 11 - 80 09) Four patients have been treated on this study. All are doing well in remission and had minimal toxicity.

The number of patients needed for this study has been accumulated group-wide and the study is considered completed. Results will be published by the Children's Oncology Study Group.

STATUS: (C)

TITLE: CCG 162 - Treatment of Newly Diagnosed Acute Lymphoblastic Leukemia for Patients with "Average Risk" Prognostic Characteristics

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/27

TECHNICAL OBJECTIVES

(1) Modification of therapy to improve remission duration and survival in children with "average risk" ALL without excessive increase in toxicity. (2) Evaluate the effect of the addition of monthly pulse doses of cyclophosphadine, adriamycin, and cytosine arabinoside to standard maintenance therapy on remission duration, and survival. (3) Evaluate the effect of periodic reinduction with vincristine, prednisone and L-asparaginase on remission duration and survival. (4) Evaluate by randomization the addition of IT methotrexate during maintenance relative to control of CNS leukemia and marrow relapse. (5) Determine if factors other than age at diagnosis and initial WBC are important risk factors. (6) Evaluate the prognostic significance of surface marker analysis (E-rosette formation and surface immunoglobulins) of leukemic blast cells at diagnosis and relapse. (7) Determine the effect of total drug dose/M²/unit time on remission duration and survival. (8) Analyze patients who relapse or die in remission for features such as intercurrent illness, deviation and lapses in therapy, and cell surface markers in an attempt to better define groups and reasons for treatment failure.

METHOD

Patients previously untreated with acute lymphoblastic or undifferentiated leukemia will be eligible. All patients will receive identical induction therapy and cranial radiation and six doses of IT MTX during intensification. Patients will be randomized to receive or not receive maintenance IT methotrexate every 84 days x 12. Patients will be further randomized to one of the following three maintenance regimens: Daily oral 6-MP, weekly oral methotrexate and pulses of vincristine and prednisone every 28 days, or the above regimen with the addition of cytosine arabinoside, cyclophosphamide or adriamycin on an alternating basis to the pulses of vincristine and prednisone; or daily oral 6-MP, weekly oral methotrexate with a 28 day reinduction with vincristine, prednisone, and L-asparaginase given every 14 days x 6. Therapy will be discontinued after 12 maintenance cycles contingent upon a continuous complete remission.

CCG 162 - Holt

PROGRESS

(79 11 - 80 09) Two patients have been treated on this study. Both are doing well in remission with no toxicity.

The study is now closed since a large enough group has been accumulated group-wide for the purposes of the study. Data are now being analyzed.

STATUS: (C)

TITLE: CCG 163 - Treatment of Newly Diagnosed Acute Lymphoblastic Leukemia for Patients with "High Risk" Prognostic Characteristics

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/28

TECHNICAL OBJECTIVES

(1) Modification of therapy to improve remission duration and survival in children with "high risk" ALL by modifying and intensifying all phases of therapy. Attempting to improve remission duration and survival by: (a) The addition of IT methotrexate during maintenance to cranial radiation and IT methotrexate for CNS prophylaxis. (b) Comparisons of two intensive maintenance regimens: (i) the addition of monthly pulse doses of cytosine arabinoside, cyclophosphamide, and adriamycin to standard maintenance therapy and (ii) repeated cyclic courses of POMP, COP, POCA, and IV methotrexate with citrovorum rescue. (2) Determine if factors other than age at diagnosis and initial WBC count are important risk factors. (3) Evaluate the prognostic significance of surface marker analysis (E-rosette formation and surface immunoglobulins) of leukemic blast cells at diagnosis and relapse. (4) Determine the effect of total drug dose/ M^2 /unit time on remission duration and survival. (5) Study patients who relapse or die in remission for intercurrent illness, deviations and lapses in therapy and the relationship of these events to extramedullary disease.

METHOD

Patients less than 21 years of age and WBC $>50,000/mm^3$ at diagnosis will be eligible. All patients will receive identical induction therapy and cranial radiation and six doses of IT MTX during intensification. All patients will receive maintenance IT MTX every 84 days \times 12. Maintenance therapy will be randomized to one of the following two regimens: (1) daily oral 6-MP, weekly oral methotrexate, and pulses of vincristine/prednisone/cytosine arabinoside; vincristine/prednisone/cyclophosphamide; and vincristine/prednisone/adriamycin given every 28 days on an alternating basis. The three separate pulses will be repeated every 84 days for 12 cycles. (2) Alternating courses of vincristine/prednisone/6-MP, methotrexate; vincristine/prednisone/cyclophosphamide; vincristine/prednisone/adriamycin/cytosine arabinoside; and intermediate dose IV methotrexate with citrovorum

CCG 163 - Holt

factor rescue every 21 days. Twelve 84 day cycles will be given. Maintenance therapy will be based on 84 day cycles. All patients will receive a minimum of 12 cycles of therapy rather than a minimum of three years of maintenance therapy. Duration of maintenance therapy has been intentionally left open-ended. When more information is available from other group studies in two to three years, action will be taken to decide when therapy should be terminated or if other therapy should be instituted. All of the studies have been statistically designed to allow an additional randomization to occur at that time if necessary to further explore this important issue.

PROGRESS

(79 11 - 80 09) No patients were registered on this study. The study is closed due to the fact that enough patients have been accumulated group-wide for statistical purposes.

STATUS: (C)

TITLE: CCG 172 - Vindesine or Vincristine Plus L'asparaginase and Prednisone for Reinduction, and Cyclophosphamide Plus Vindesine or Vincristine for Maintenance in the Treatment of Recurrent Acute Lymphocytic Leukemia in Children - Patients Relapsing from Other Studies, Phase III.

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/32

TECHNICAL OBJECTIVES

To compare the relative effectiveness of vindesine and vincristine in inducing remission when used with standard prednisone and L'asparaginase; to determine the relative degrees of neurotoxicity of vindesine compared to vincristine; to determine the relative degree of thrombocytosis/leukopenia induced by vindesine compared to vincristine; to determine whether there is cross-resistance between vincristine and vindesine; and to provide data concerning the need for synchronizing timing of vinca alkaloid injections in relation to cyclophosphamide in order to determine relative length of remission.

METHOD

Patients with recurrent acute lymphocytic leukemia relapsing from other chemotherapeutic studies will be eligible. There will be two induction treatments depending upon whether vindesine (VND) or vincristine (VCR) is used. VND, L'asparaginase, and prednisone will be used for patients with VCR resistance. VCR non-resistant patients will be randomized to be treated with either VND, L'asparaginase, and prednisone or VCR, L'asparaginase, and prednisone. Patients with M₃ on day 28 will go off study. Maintenance therapy will begin on day 28. Patients will be randomized to one of six maintenance regimens based upon induction therapy. Regimen 1 will consist of cyclophosphamide (CPM) and VND, with VND administered 24 hours before CPM for VCP resistant patients. Regimen 2 will be the same as Regimen 1, but for VCR non-resistant patients. Regimen 3 will consist of CPM and VND with VND administered concurrent with CPM for VCR resistant patients. Regimen 4 will be the same as Regimen 3, but for VCR non-resistant patients. Regimen 5 will consist of CPM and VCR with VCR administered 24 hours before CPM for VCR non-resistant patients. Regimen 6 will consist of CPM and VCR with VCR administered concurrent with CPM for VCR non-resistant patients.

CCG 172 - Holt

PROGRESS

(80 02 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: CCG 191P - Total Sanctuary vs Conventional CNS Treatment of Newly Diagnosed Acute Lymphoblastic Leukemia for Patients with "Average Risk" and "High Risk" Prognostic Characteristics, Phase III

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/89

TECHNICAL OBJECTIVE

To compare the effects of high-dose, protracted IV methotrexate infusions vs standard cranial irradiation plus IT methotrexate on: (1) central nervous system relapse; (2) central nervous system toxicity - both acute and delayed; (3) hematologic remission induction and duration; (4) non-CNS extramedullary relapse (e.g., testes); and (5) survival.

METHOD

Previously untreated patients less than 21 years of age with acute lymphoblastic leukemia who are (1) less than 3 years old, (2) 7 years of age or older, or (3) have an initial WBC of greater than 10,000/ μ l will be eligible. Patients with the diagnosis of acute undifferentiated leukemia on any initial WBC will be treated on this protocol but analyzed as a separate group. Patients will be treated initially with prednisone, vincristine, L-asparaginase, daunomycin, and central nervous system prophylaxis. The type of CNS prophylaxis will be determined by randomization and will consist either of very high doses of methotrexate IV or cranial radiation plus IT methotrexate. Most of the CNS therapy will be given during the second month of treatment, during which 6-MP will replace the daunomycin and L-asparaginase. From the third month on, remission will be maintained by a sequence of multiple drug administrations, including vincristine, prednisone, L-asparaginase, daunomycin, methotrexate, cyclophosphamide, and 6-MP. M₃ bone marrow or extramedullary leukemia at any time will be cause for removal from the study.

PROGRESS

(79 11 - 80 09) One patient was treated and did well until relapse at one year with CNS leukemia when he was removed from the study.

STATUS: (0)

TITLE: CCG 372 - Evaluation of Cis-Platinum Diamine Dichloride (CPDD) and 4'-Demethyl-Epidophyllotoxin- β -D-Thenylidene Glucoside (VM-26) for the Treatment of Recurrent Stage IV Neuroblastoma of Childhood, Phase II.

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/35

TECHNICAL OBJECTIVE

To determine if CPDD and VM-26, both of which have been reported to produce responses in recurrent Stage IV neuroblastoma as single agents, are efficacious when given in combination.

METHOD

Patients, to be eligible, must have Stage IV neuroblastoma, i.e., remote disease involving skeleton, marrow, soft tissues, distant lymph nodes, etc. Patients previously treated with CPDD and/or VM-26 are not eligible. VM-26, 150 mg/M² IV, will be administered on days 1, 8, and 15. CPDD, 4.5 mg/kg IV, will be administered on day 2 (24 hours after day 1 dose of VM-26). Patients will be hospitalized. Cycles will be repeated every three weeks. Two complete cycles will be considered an adequate trial. If a complete or partial response is noted, cycles will be continued until progressive disease ensues.

PROGRESS

(80 06 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: CCG 541 - Comparison of Involved Field Radiotherapy with Involved Field Radiotherapy Plus Adjuvant Chemotherapy (MOPP: Mechlorethamine, Vincristine, Procarbazine, Prednisone) and Extended Field Radiotherapy in the Treatment of Stage I and II Hodgkin's Disease in Children

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/38

TECHNICAL OBJECTIVES

To compare the effectiveness of involved field (IF) radiotherapy, IF radiotherapy followed by MOPP chemotherapy, and extended field (EF) radiotherapy in treating laparotomy confirmed Stage I and II Hodgkin's disease in children in terms of (a) duration of disease-free interval following completion of initial therapy, (b) the type and extent of disease extensions following initial therapy, and (c) survival. To determine the retrievability of new disease following primary therapy for each of the three regimens, using specified retrieval plans.

To determine the effect of specific histology on results of primary and retrieval therapy for each of the three regimens.

To determine the comparative effects of the three treatment regimens with respect to: (a) linear growth, bi-acromial, and bi-cristal diameters, (b) incidence of hypothyroidism and sterility, (c) incidence of second malignancies, (d) complications following staging celiotomy and splenectomy, immediate and remote, including fulminating infections, and (e) effectiveness of penicillin prophylaxis in the prevention of post-splenectomy infectious complications.

METHOD

Children with laparotomy confirmed Stage I and II Hodgkin's disease with no prior exposure to chemotherapy will be eligible. Patients will be randomized to three groups. Regimen I will consist of IF radiotherapy followed by IF radiotherapy plus MOPP q 28 days x 6 on first relapse. Regimen II will consist of EF radiotherapy followed by complete EF + MOPP q 28 days x 6 on first relapse. Regimen III will consist of IF + MOPP q 28 days x 6 followed by IF + MOPP q 28 days x 6 on first relapse. Patients will be removed from the study on documentation of second relapse.

CCG 541 - Holt

PROGRESS

(80 05 - 80 09) No patients were registered on this protocol.

STATUS: (0)

TITLE: CCG 551 - A Trial of Memorial Hospital LSA₂-L₂ Treatment Regimen (Modified) Cyclophosphamide, Vincristine, Prednisone, Methotrexate, and Daunomycin for Induction; Cytosine Arabinoside, 6-Thioguanine, L-Asparaginase, Methotrexate, and BCNU for Consolidation; and 6-Thioguanine, Hydroxyurea, Cytosine Arabinoside, and Methotrexate for Maintenance vs Intermittent High Dose Cyclophosphamide, Moderate Dose Methotrexate, Vincristine, and Prednisone (COMP) and Radiation Therapy for the Treatment of Non-Hodgkin's Lymphoma in Children, With a Study of Disease Characterization, Phase III.

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/36

TECHNICAL OBJECTIVES

To study the classification and biology of that group of childhood neoplasms included in the non-hodgkin's lymphomas. To compare the effectiveness of two combination chemotherapy programs (Memorial Hospital LSA₂-L₂ and COMP) in the control of all forms of childhood non-hodgkin's lymphoma. To determine for each of the two treatment regimens the effectiveness of standardised IT methotrexate without radiation for the control of occult CNS disease. To determine for each of the treatment regimens the effectiveness of standardised irradiation of bulk disease.

METHOD

All newly diagnosed and previously untreated patients with non-Hodgkin's lymphoma will be eligible. Multi-disciplinary treatment of the patient is required in this study. Surgical treatment will be undertaken first. For most patients this will be a biopsy procedure, but for abdominal presentation, major tumor resection may be necessary. Following the surgical phase of treatment and the initial evaluation, treatment will commence with combined chemotherapy and irradiation by random choice between Regimen I or Regimen II (see title for drugs in each regimen). Irradiation will commence during induction upon bone marrow recovery. In general, irradiation will be completed before consolidation or maintenance has commenced according to regimen. Treatment will terminate on completion of 18 months of treatment. All patients will be followed for a minimum of 5 years or until death.

CCG 551 - Holt

PROGRESS

(80 06 - 80 09) Two patients are currently on this study.
Both are responding well with some nausea and vomiting.

STATUS: (0)

TITLE: CCG 84 - Histiocytosis X: A Study of the Biology, Clinical, and Histologic Staging, Treatment, and Prognosis in Previously Untreated Children, Phase III.

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 79/37

TECHNICAL OBJECTIVES

To determine if multidrug induction and maintenance regimens will improve survival in the young high-risk patient and reduce sequelae in the long-term survivors. To obtain comprehensive immunologic studies at diagnosis and at critical times during the course of the disease so as to (a) identify patients with primary immunodeficiency disorders which may simulate histiocytosis X, (b) determine if patients with histiocytosis X less than 3 years of age have acquired defects in T and B lymphocyte function, and (c) ascertain if either stage of disease or survival of these young patients can be correlated with T and B lymphocyte function. To continue to collect clinical and histologic data so that patients may be staged in a prospective fashion into those with and without organ dysfunction and those with benign or malignant histology. In addition, more detailed pathologic studies will be recommended so as to increase knowledge of the cellular infiltrates in various tissues.

METHOD

Patients 15 years of age or less with a histologic diagnosis of histiocytosis will be eligible. Patients with only a solitary bone lesion or with only two or three small well localized bone lesions or with primary immunodeficiency disease will be excluded. Induction will consist of 17 weeks of chemotherapy including prednisone, vinblastine, methotrexate, and cyclophosphamide. For purposes of evaluating the response to therapy, an adequate trial will be at least 4 weeks of therapy. If the patient achieves complete (CR) or partial remission (PR) at 17 weeks of induction, then maintenance therapy for six months will consist of methotrexate, cyclophosphamide, and 6-MP. If there is recurrence, the 4-drug regimen will be repeated. Radiation for localized disease may be used for lesions not controlled by chemotherapy so long as other parameters of measurements of response are available.

CCG 984 - Holt

PROGRESS

(80 05 - 80 09) No patients were registered on this study.

STATUS: (0)

PEDIATRIC BRANCH ONCOLOGY PROTOCOLS
NATIONAL CANCER INSTITUTE

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AD-A100 955

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TITLE: Intrathecal Aminopterin, NSC #739-NB, Clinical Brochure

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 80/50

TECHNICAL OBJECTIVES

To demonstrate that IT aminopterin is less neurotoxic in man than IT methotrexate. To show that IT aminopterin requires fewer lumbar punctures for an equivalent therapeutic effect than IT methotrexate. To compare the pharmacokinetics in man of IT aminopterin and IT methotrexate.

METHOD

Any patient with a CNS neoplasm, primary or metastatic, will be eligible provided IT methotrexate is an accepted treatment for the neoplasm. Patients with acute leukemia or non-Hodgkin's lymphoma scheduled to receive preventive IT chemotherapy will be eligible. Patients with a prior history of IT methotrexate arachnoiditis will be eligible, but patients with a prior history of myelopathy or encephalopathy associated with IT methotrexate therapy will not be eligible. Eligible patients will receive intralumbar AMT at a dose of 2.0 mg per injection at weekly intervals. For prophylaxis, six injections will be given. For treatment of established disease, the injections will be continued until the CSF is free of blast cells by cytocentrifuge analysis. Thereafter, the injections will be given weekly x 2, then q 2 weeks x 2, then monthly for 2 years.

PROGRESS

(80 09 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: POB 77/03 - Treatment of Metastatic Osteosarcoma

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 80/51

TECHNICAL OBJECTIVES

To determine the differences in tumor response rates and drug toxicities when high dose methotrexate is given as a 6-hour bolus infusion or as a 42-hour infusion. To determine if the use of intensive chemotherapy given when tumor burden is minimal results in the complete eradication of all microscopic foci of metastatic osteosarcoma.

METHOD

Patients <30 years of age with no evidence of serious infection, active bleeding disorders, or concomitant significant complications and biopsy proven osteosarcoma are eligible. Patients must have pathologic or radiologic evidence of overt metastatic disease and must have received no previous chemotherapy, radiotherapy, or surgical therapy for metastatic disease. Patients presenting with metastatic osteosarcoma will enter a first phase which is designed to create a state in which there is no evidence of disease (NED). If possible, this will be achieved by surgery alone; if surgery alone cannot achieve NED, then chemotherapy will be used initially rather than surgery. Patients in this latter category will be randomized to receive weekly vincristine plus high dose MTX-CF given over 6 hours or methotrexate given as a 42-hour infusion. Patients who respond to this phase of methotrexate may become candidates for surgery even though resection was not possible initially. If NED can be achieved in this way, patients will proceed to Phase 2. Patients achieving NED with surgery and/or chemotherapy will enter Phase 2 of the protocol and be treated with intensive combination chemotherapy employing agents known to be active against overt metastatic disease (methotrexate, citrovorum factor, vincristine, adriamycin, cyclophosphamide, phenylalanine mustard, DTIC, cis-platinum).

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PROGRESS

(80 09 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: POB 77/04 - Childhood Non-Hodgkin's Lymphoma

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 80/62

TECHNICAL OBJECTIVES

To treat patients in as uniform a manner as possible while studying the spectrum of diseases in as much detail as possible, including clinical features, histology and cytology, surface markers, induction of differentiation in vitro, functional potential of tumor cells, distribution patterns of DNA and protein pre- and post-treatment, and possible tumor markers. From such studies, it is hoped that insights into classification and rational approaches to therapy will be forthcoming.

METHOD

Untreated patients with non-Hodgkin's lymphoma under 25 years of age, or with Brukitt's lymphoma at any age, who consent to a second biopsy procedure are eligible. Patients in whom a diagnosis of non-Hodgkin's lymphoma is strongly suspected will be admitted as soon as possible. Treatment will be commenced as soon as initial studies and biopsy have been completed and therapy should begin within 48-72 hours. Therapy will include total surgical resection wherever possible. The backbone of therapy, however, will be chemotherapy, since childhood non-Hodgkin's lymphoma is rarely a localized tumor. Drug therapy will be intensive utilizing cyclophosphamide, vincristine, adriamycin, methotrexate, and prednisone. These will be used in a sequence which should result in drugs being administered every 10 days. We propose a somewhat different approach to prophylactic therapy, in that first, an IT methotrexate boost will be given during IV 42 hour methotrexate infusion; second, Ara-C will be used as a second drug in combination with methotrexate, and third, prophylaxis will begin at the same time as systemic therapy since it is more likely that tumor cells enter the sanctuary at a time when the systemic tumor burden is high. Irradiation as part of CNS prophylactic therapy is not planned.

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PROGRESS

(80 09 - 80 09) No patients were registered on this protocol.

STATUS: (0)

TITLE: POB 77/05 - Treatment of Metastatic and High Risk Ewing's Sarcoma

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 80/52

TECHNICAL OBJECTIVES

To examine the efficacy of total body irradiation in combination with high dose chemotherapy in the treatment of metastatic or high-risk Ewing's sarcoma. To examine the immunological status of patients receiving total body irradiation as a function of time. To examine the utility of autologous marrow infusion in patients receiving high-dose chemotherapy who do not have marrow disease at presentation but who may have metastatic disease in other sites.

METHOD

Patients with a pathologically proven diagnosis of Ewing's sarcoma presenting with metastatic disease or with a pelvic or vertebral primary lesion, without prior radiation or chemotherapy, will be eligible. Chemotherapy to include vincristine, actinomycin D, and cyclophosphamide will be given for four weeks concomitant with irradiation to the primary site for 5 weeks. Total body irradiation will then be given weeks 6-10. High dose therapy of vincristine, adriamycin, cyclophosphamide, and DTIC will then be given for 3 days. Maintenance chemotherapy to include vincristine, adriamycin, cyclophosphamide, and DTIC will be given once every 6 weeks for 12 cycles.

PROGRESS

(80 09 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: POB 77/06 - Treatment of Low Risk Ewing's Sarcoma

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 80/53

TECHNICAL OBJECTIVES

To evaluate the efficacy of prophylactic pulmonary irradiation in conjunction with combination chemotherapy in the treatment of low risk Ewing's sarcoma. To evaluate the immunologic status and competence of patients with Ewing's sarcoma as a function of time.

METHOD

Patients with a pathologically proven diagnosis of Ewing's sarcoma presenting with distal primary lesions (but not in the pelvis or spine) without evidence of metastatic disease are eligible for this study. Patients with prior chemotherapy, radiation therapy, or surgical resection procedures other than biopsies are ineligible for the study. For initial therapy, patients will receive vincristine, actinomycin D, and cyclophosphamide (given week 1 and 4), radiation therapy to the primary site (5 treatments/week for 5 weeks), and subsequent to the completion of radiation to the primary site, pulmonary irradiation (5 treatments/week for 2 weeks). Maintenance chemotherapy will begin subsequent to pulmonary irradiation consisting of vincristine, adriamycin, and cyclophosphamide every 4 weeks for a total of 12 courses.

PROGRESS

(80 09 - 80 09) No patients were registered on this protocol.

STATUS: (0)

TITLE: POB 77/11 - A Prospective Randomized Trial of the Utility of HLA-Matched Platelet Transfusions for the Support of Thrombocytopenic Cancer Patients

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 80/54

TECHNICAL OBJECTIVES

To determine what differences exist between patients initially treated with HLA-matched or HLA-mismatched platelets in the number and frequency of transfusions required; mean increments of those transfusions; frequency of transfusion reactions; number of bleeding episodes; development of anti-HLA antibodies; and length of time until patients become refractory to the treatment strategy employed. To determine how often patients refractory to one strategy will respond to the other and what differences will exist in those subsequent responses. To determine if the order of strategy makes a difference in the total length of time patients respond to platelet transfusions. To determine if the type of platelets transfused in those patients refractory to both matched and mismatched platelet transfusions makes a difference in the number of transfusions required, the mean increments of those transfusions, and the frequency and time to the development of significant bleeding episodes.

METHOD

All pediatric patients admitted to Madigan will be eligible for this study. Patients will be specifically excluded if they have received more than 5 blood component transfusions, they cannot be HLA type, or they have an inadequate number of HLA-matched donors to provide HLA-matched platelet support. Patients will be randomised into 2 groups by diagnostic categories; further, patients within each diagnostic category will be divided into those with and without known bone marrow involvement. Group 1 patients will receive platelet transfusions with matched platelets. Group 2 will receive mismatched platelets. The indications for transfusion will be the same in both groups. Patients in both groups will continue to receive platelet transfusions until the patient is judged to be refractory and then crossed into the opposite group. When patients are considered refractory to matched and mismatched platelets, they shall be randomized to receive either matched

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or mismatched platelets for the remainder of the study. Following randomization, the patients will continue to receive the assigned platelet preparation until the development of a significant bleeding problem. Patients refractory to both matched and mismatched platelets who develop significant bleeding problems will be considered off-study and will be supported with the best available platelet support.

PROGRESS

(80 09 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: POB 78/06 - Treatment of Recurrent Lymphoma

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 80/55

TECHNICAL OBJECTIVES

To investigate the utility of a combination of aggressive chemotherapy and total body irradiation (TBI) in the treatment of recurrent disseminated non-Hodgkin's lymphoma. To study the utility of flow-micro-fluorimetric techniques as a potential means of individualizing timed-sequence chemotherapy scheduling. To study the value of supplementary irradiation to apparently localized recurrent tumor. To study recurrent tumor for changes in morphology, surface receptors, EBV genome, and cell surface micro-viscosity as compared to the patient's primary tumor.

METHOD

Patients with recurrent non-Hodgkin's lymphoma who have relapsed on other protocols in whom autologous marrow has been stored at least 2 months prior to relapse and whose disease is not defined as small volume, local relapse will be eligible for the study. The presence of complicating factors (renal failure, infection, etc) which constitute relative contraindications to the initiation of CARAT therapy (Cytoxan, ARA-C, TBI) will be considered individually for eligibility. Patients with prior CNS disease of proven resistance to chemotherapy and cranial or craniospinal irradiation will normally be ineligible for CARAT therapy. All patients will be treated in laminar flow rooms if available. Normally, chemotherapy will not commence until the total WBC is >4000 and granulocyte count >1500 in order to keep the period of granulocytopenia to a minimum. All patients will be vigorously hydrated prior to therapy. Treatment schemas are: cytoxan: 45 mg/kg days 1, 2, 3, 4, (IV in 100 cc D5W over 30 min; TBI: 15 rads daily x 8 commencing on day 1 omitting weekends or 400 rads on days 6 and 8; ARA-C: 300 mg/M²/24 hours by continuous infusion days 9, 10, 11, 12, given in 5% dextrose/water; autologous marrow infusion: day 13. In the presence of CNS disease, intrathecal or intraventricular therapy will be administered. Patients also may be randomized to receive hyperalimentation.

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PROGRESS

(80 09 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: POB 78/10 - A Phase II Study of Achromobacter Glutaminase
in Acute Leukemia

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 80/56

TECHNICAL OBJECTIVES

To determine the therapeutic efficacy of glutaminase against acute leukemia refractory to standard agents. To determine the toxicity of glutaminase administered in a fixed dosage schedule.

METHOD

Patients must have a life expectancy of least 4 weeks and cytologically documented acute lymphocytic, acute myelocytic, or acute undifferentiated leukemia (on bone marrow aspirate or biopsy specimen). In addition, patients must be proven refractory to conventional drugs considered active against their disease and must have recovered from the toxic effects of any previous therapy. The drug will be administered as a continuous infusion (10,000 IU/M²/day) for at least 14 days with re-evaluation of the leukemia at that time. If no beneficial effect has been seen the trial will be discontinued. If there is evidence of improvement, the infusion will be continued for a total of 28 days.

PROGRESS

(80 09 - 80 09) No patients have been registered on this study.

STATUS: (0)

TITLE: POB 78/13 - Fever and Antimicrobial Therapy, Study II

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 80/64

TECHNICAL OBJECTIVES

To evaluate the role of empiric antibiotic therapy in granulocytopenic cancer patients. To reduce the incidence of fever and infection in patients for whom treatment related granulocytopenia is anticipated. To evaluate and treat the granulocytopenic patient colonized with fungi.

METHOD

Patients in this study will be treated in three distinct groups. Group I (Treatment of Granulocytopenic Patients Prior to the Onset of Fever) will consist of afebrile patients receiving chemotherapy anticipated to produce granulocytopenia, irrespective of the projected duration of granulocytopenia. These patients will be randomized to a double blind study of either erythromycin and bactrim or a placebo. Group II (Evaluation and Treatment of Granulocytopenic Patients Who Become Febrile) will consist of patients with granulocytopenia who are febrile with either a documented infection or a fever of undetermined origin. Those with documented infection will receive either broad spectrum antibiotics or specific therapy based on sensitivity testing. FUO patients will be treated with empiric antibiotics for 7 days and then managed according to their status (febrile/afebrile). Group III (Evaluation and Treatment of the Granulocytopenic Patient Colonized with Fungi), after 7 days of KGC will be randomized to receive amphotericin or not receive amphotericin.

PROGRESS

(80 09 - 80 09) No patients were registered on this protocol.

STATUS: (0)

TITLE: POB 79/01 - Evaluation of Human Lymphoblastoid Interferon and Poly I:C (Stabilized with Poly-L-Lysine and Carboxymethyl Cellulose (Poly{ICLC})) in the Treatment of Acute Myelocytic Leukemia, CLL, and Various Solid Tumors, Phase II.

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 80/57

TECHNICAL OBJECTIVES

To determine the therapeutic efficacy of human lymphoblastoid interferon and stabilized polyribonucleic acid-polyribocytidyl acid (poly{ICLC}) in patients with acute myelocytic leukemia (who are in their first bone marrow relapse and have received no previous induction treatment for this relapse), and in patients with various solid tumors in relapse.

METHOD

Patients 16 or over with acute myelocytic leukemia who are in their first bone marrow relapse after having been treated with standard drugs, and who have not received any other induction treatment for this relapse, are eligible. Solid tumor patients in relapse are eligible as determined by the specific protocol priority scheme for that tumor type. Patients will be randomized to receive either lymphoblastoid interferon or Poly (ICLC). An adequate trial will consist of a minimum of one month of treatment. A second month of induction with the same agent on the same schedule will be given if marrow improves by day 30 from M₃ to M₂ in the case of AML, or if, in the case of solid tumor patients, the disease is stable or improved. In no case will induction continue beyond two months. Patients with stable or improving disease at the end of two months will begin a maintenance schedule with the same agent; patients with progressive disease at the end of one or two months may, if their condition permits, cross-over to an induction attempt with the other agent.

PROGRESS

(80 09 - 80 09) No patients were registered on this study.

STATUS: (0)

TITLE: POB 79/03 - Phase II Study of 2'-Deoxycosformycin in
Acute Lymphoblastic Leukemia

PRINCIPAL INVESTIGATOR: LTC Charlene P. Holt, MC

PROFESSIONAL ASSISTANT: MAJ Alan D. Mease, MC

WORK UNIT NO: 80/58

TECHNICAL OBJECTIVES

To determine the therapeutic efficacy of 2'-deoxycosformycin against acute lymphoblastic leukemia refractory to standard agents. To determine the toxicity of 2'-deoxycosformycin (2'dCF) administered in a fixed dosage schedule.

METHOD

Patients with a life expectancy of at least 4 weeks who have cytologically documented acute lymphoblastic leukemia on bone marrow aspirate or biopsy specimen are eligible. Patients must be proven refractory to those conventional drugs considered active against ALL. This protocol will investigate a dose of 0.25 mg/kg 2'dCF given IV daily for 3 consecutive days. Each patient will receive at least 2 courses of 2'dCF (toxicity permitting). The second course of 2'dCF will be given 14 days following the initial treatment. If there is no evidence of improvement on day 28 the patient will be removed from the study. Patients who have achieved either a complete or partial response after the second course will continue to receive treatment on this protocol until M₃ marrow status occurs. Upon entrance to the protocol, cell surface marker studies will be obtained on the lymphoblasts from each patient. The ALL patients will be treated and analyzed separately according to whether they have T cell or non-T cell ALL.

PROGRESS

(80 09 - 80 09) No patients were registered on this study.

STATUS: (0)

APPENDIX I

GUIDING PRINCIPLES OF THE CARE AND USE OF ANIMALS

Approved by the Council
of The American Physiological Society

Only animals that are lawfully acquired shall be used in this laboratory, and their retention and use shall be in every case in strict compliance with state and local laws and regulations.

Animals in the laboratory must receive every consideration for their bodily comfort; they must be kindly treated, properly fed, and their surroundings kept in a sanitary condition.

Appropriate anesthetics must be used to eliminate sensibility to pain during operative procedures. Where recovery from anesthesia is necessary during the study, acceptable technic to minimize pain must be followed. Curarizing agents are not anesthetics. Where the study does not require recovery from anesthesia, the animal must be killed in a humane manner at the conclusion of the observations.

The postoperative care of animals shall be such as to minimize discomfort and pain, and in any case shall be equivalent to accepted practices in schools of veterinary medicine.

When animals are used by students for their education or the advancement of science such work shall be under the direct supervision of an experienced teacher or investigator. The rules for the care of such animals must be the same as for animals used for research.

APPENDIX II

Recommendations from the Declaration of Helsinki

I. Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.
2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.
3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.
5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

II. Clinical Research Combined with Professional Care

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, reestablishing health, or alleviating suffering.

If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity, the permission of the legal guardian replaces that of the patient.

2. The nature, the purpose, and the risk of clinical research must be explained to the subject by the doctor.
3. a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.
b. The subject of clinical research should be in such a mental, physical, and legal state as to be able to exercise fully his power of choice.

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